FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH (CDER)

Joint Meeting of the Anesthetic and
Life Support Drugs Advisory Committee (ALSDAC) &
Drug Safety and Risk Management
Advisory Committee (DSaRM)

THURSDAY, JULY 22, 2010

8:00 a.m. to 5:00 p.m.

UMUC Conference Center at the Marriott

Adelphi, Maryland

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Chief Executive and Secretary
Accreditation Council for Continuing Medical Education
Chicago, Illinois

Peter Vlasses, Pharm.D., D.Sc. (Hon.)
Executive Director
Accreditation Council for Pharmacy Education
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FDA MEETING PARTICIPANTS AT THE TABLE (NON-VOTING)

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CDER, FDA

Gerald Dal Pan, M.D.
Director, Office of Surveillance and Epidemiology
CDER, FDA

John Jenkins, M.D.
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CDER, FDA

Bob Rappaport, M.D.
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Deputy Director for Regulatory Programs
CDER, FDA

I N D E X

I N D E X (continued)

I N D E X (continued)

P R O C E E D I N G S

(8:00 a.m.)

DR. KIRSCH: Good morning, everybody. We're going to get the meeting started now. So I'd like to officially call to order this meeting to order. This is the FDA's Center for Drug Evaluation and Research Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee for July 22nd and tomorrow, July 23rd.

The first thing we'll do is introduce the members of the committee, and we'll start with Dr. Tortella over in the corner there.

DR. TORTELLA: Bartholomew Tortella, industry representative.

DR. BICKEL: Warren Bickel, University of Arkansas for Medical Sciences.

DR. KRANTZ: Mori Krantz, cardiology, University of Colorado.

DR. MARKMAN: John Markman, neurology and pain management, University of Rochester, Rochester, New York.

DR. GRAY: Roland Gray. I'm the medical director of the Physicians Health Program in Tennessee.

DR. BOYER: Edward Boyer, medical toxicology, University of Massachusetts.

DR. WOODS: Mark Woods, pharmacy department, St. Luke's Hospital in Kansas City, Missouri.

DR. TERMAN: Greg Terman, anesthesiology and pain medicine, University of Washington, Seattle.

DR. BRULL: Sorin Brull, anesthesiologist at Mayo Clinic College of Medicine.

DR. HATSUKAMI: Dorothy Hatsukami, School of Medicine, University of Minnesota.

DR. CARTER: Lawrence Carter, psychiatry and pharmacology at University of Arkansas for Medical Sciences.

MS. KRIVACIC: Susan Krivacic, patient representative, Austin, Texas.

DR. COVINGTON: Ed Covington, Cleveland Clinic, Cleveland, Ohio, Neurological Center for Pain.

DR. VAIDA: Allen Vaida, a pharmacist from Institute for Safe Medication Practices.

DR. MICHNA: Ed Michna, anesthesia, pain management at Brigham and Women's Hospital in Boston.

DR. KERNS: Bob Kerns, psychologist, VA Connecticut Healthcare System in West Haven, Connecticut and Yale University.

DR. MORRATO: Elaine Morrato, Department of Health Systems Management and Policy at the Colorado School of Public Health, University of Colorado Denver.

DR. KHUC: Kristine Khuc, designated federal official.

DR. KIRSCH: Jeff Kirsch, Department of Anesthesiology, Oregon Health Science University.

DR. FARRAR: John Farrar, neurologist and pain and epidemiologist at the Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania.

DR. NELSON: Lewis Nelson, emergency medicine and medical toxicology at New York University School of Medicine.

DR. OLBRISCH: Mary Ellen Olbrisch, clinical health psychologist and professor psychiatry and

surgery, Virginia Commonwealth University.

DR. TODD: Knox Todd, emergency medicine, Albert Einstein College of Medicine, New York.

DR. PEAIRS: Carol Peairs, anesthesiology and pain medicine, Phoenix VA Healthcare Systems.

DR. CRAIG: I'm Dave Craig, a clinical pharmacist specialist at Moffitt Cancer Center in Tampa, Florida.

DR. WOLFE: Sid Wolfe, internist with the health research group at Public Citizen.

DR. DESHPANDE: Jay Deshpande, I'm a pediatric anesthesiologist and intensivist from Vanderbilt University.

DR. PORTER: Linda Porter, National Institute of Neurological Disorders and Stroke at the NIH.

DR. FLICK: Randall Flick, pediatric anesthesiology and intensive care at Mayo Clinic.

DR. BEARDLSEY: Patrick Beardsley, professor of pharmacology and toxicology, Virginia Commonwealth University.

DR. MORRIS-KUKOSKI: Cynthia Morris-Kukoski.

I'm a forensic examiner in toxicology at the FBI laboratory in Quantico, Virginia and a clinical pharmacist toxicologist for the United States Navy Reserve.

DR. RAPPAPORT: Bob Rappaport, director of the Division of Anesthesia and Analgesia at FDA.

DR. DEL PAN: Gerald Del Pan, director of the Office of Surveillance and Epidemiology at FDA.

DR. JENKINS: John Jenkins, director of the Office of New Drugs at FDA.

MS. AXELRAD: Jane Axelrad, associate director for policy, CDER, FDA.

DR. THROCKMORTON: Doug Throckmorton, deputy director, Center for Drug Evaluation and Research, FDA.

DR. KIRSCH: There are several people who came to the table after their introduction has passed their spot, so I'll give them a second to introduce themselves.

DR. BERGER: Ann Berger, pain and palliative care, National Institutes of Health, clinical center.

DR. KOSTEN: Tom Kosten, professor of

psychiatry, pharmacology, neuroscience at Baylor College of Medicine, Houston, Texas and at the MD Anderson Cancer Center, epidemiology and psychiatry.

DR. BALLANTYNE: Jane Ballantyne, professor of anesthesia and pain medicine at the University of Pennsylvania in Philadelphia.

DR. KIRSCH: Dr. Turk?

DR. TURK: Dennis Turk, University of Washington.

DR. KIRSCH: One more person.

DR. WOODS: Jim Woods, Department of Pharmacology, University of Michigan.

DR. KIRSCH: I'd like to thank all the members of the committee for taking the time to come to this important meeting to discuss a very important topic.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without

interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the Chair. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting. We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusions. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch.

Before we begin, I would like to remind the committee members that we are seeing your individual perspective on the issues under discussion, not the organizational perspective of any particular group or special interest. I'd also like to remind members of the committee and members of the audience to please silence your pagers and your cell phones.

Dr. Khuc.

DR. KHUC: The Food and Drug Administration is convening today's meeting of the Anesthetic and Life Support Drugs and Drug Safety and Risk Management advisory committees under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members of the committees are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of the committees' compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 U.S.C. Section 208 and Section 712 of the Federal Food, Drug and Cosmetic Act, is being provided to participants in today's meeting and to the public. FDA has determined that members and temporary voting members of these committees are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to

special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest. Under Section 712 of the Federal Food, Drug and Cosmetic Act, Congress has authorized FDA to grant waivers to special government employees and regular federal employees with potential financial conflicts when necessary to afford the committee essential expertise.

Related to discussions of today's meeting, members and temporary voting members of these committees have been screened for potential financial conflicts of interests of their own as well as those imputed to them, including those of their spouses or minor children and for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, writing, speaking, patents and royalties and primary employment.

Today's agenda involves discussions of risk

evaluation and mitigation strategies, REMS, for extended-release and long-acting opioid analgesics. As part of the materials for the meeting, FDA anticipates presenting a proposal for a wide-class opioid REMS and will solicit feedback from the advisory committee and public on the components of that proposal. The need for adequate pain control is an element of good medical practice. In this context, some persons suffering from pain need access to potent opioid drug products. However, inappropriate prescribing, addiction and death due to prescription opioid abuse and misuse have been increasing over the last decade. This is a particular matters meeting during which general issues related to the risk evaluation and mitigation strategies for extended-release and long-acting opioid analgesics will be discussed.

Based on the agenda for today's meeting and all the financial interests reported by the committee members and temporary voting members, a conflict of interest waiver has been issued in accordance with 18 U.S.C. Section 208(b)(3) and Section 12(c)(2)(b) to

Dr. Knox Todd for serving on an advisory board for an affected firm. His participation in this advisory board may involve targets for analgesic development, including products such as extended-release and long-acting opioids and competing products and the impact of REMS on these products. The magnitude of his interest is 5,001 to 10,000 per year. The waiver allows Dr. Todd to participate fully in today's deliberations. FDA's reasons for issuing the waiver are described in the waiver document, which are posted on FDA's website at www.fda.gov/advisorycommittees/committeesmeetingmaterials/drugs. Copies of the waiver may also be obtained by submitting a written request to the agency's Freedom of Information office, Room 630 of the Parklawn Building. A copy of this statement will also be available for review at the registration table during the meeting and will be included as part of the official transcript.

To ensure transparency, we encourage all standing members and temporary voting members to disclose any public statements that they have made concerning the issues before the committees.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Bartholomew Tortella is participating in this meeting as a nonvoting industry representative acting on behalf of regulated industry. Dr. Tortella's role at this meeting is to represent industry in general and not any particular company. Dr. Tortella is employed by Novo Nordisk.

We would like to remind members and temporary voting members that if the discussions involve any of the products, firms or issues not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participant needs to exclude themselves from such involvement and their exclusion will be noted for the record.

FDA encourages all participants to advise the committees of any financial relationships that they may have with any firms at issue. Thank you.

DR. KIRSCH: Than you. We'll now proceed with the FDA opening remarks, Dr. John Jenkins.

DR. JENKINS: Thank you, Mr. Chairman, and

members of the committee.

Today's meeting represents an important milestone in FDA's ongoing efforts to manage the risk of misuse and abuse of sustained-release and long-acting opioid products. As you all know, misuse and abuse of prescription opioids is a growing societal problem that has many causes, some of which are within the scope of FDA's authority and some of which are not. About a year and a half ago, FDA decided to exercise its new authority under the Food and Drug Administration Amendments Act of 2007, commonly referred to as FDAAA, to require risk evaluation and mitigation strategy or REMS for this class of drugs. We recognized that we would need to strike a careful balance in that REMS program in our efforts in order to have a positive impact on the growing problem of misuse and abuse of these products while at the same time, avoiding unintended consequences of adversely impacting on access to these drugs for patients with chronic pain with legitimate needs.

We also recognize that before imposing a

REMS on such a broad class of drugs that is prescribed by nearly every medical specialty and used by millions of patients each year, that we needed to gain input from the many stakeholders with an interest in this issue.

That is why we have pursued a deliberate course to gain public input via numerous stakeholder meetings, a two-day public meeting last summer, an open docket after the public meeting to which we received over 2,000 comments, another public meeting last December at which we heard feedback from the industry working group, all leading up to today's two-day advisory committee meeting of the joint committee.

I can assure you that we have carefully considered the input from all the stakeholders that we have received, and we have tried to take that input and develop a REMS proposal that we believe will have a positive impact on the misuse and abuse of sustained-release and long-acting opioid products without unduly burdening the healthcare system or adversely impacting on the access to drugs for patients who need them.

Today's meeting is another opportunity for us to hear feedback from members of the committee, the manufacturers of the products and the public on how well you think we have done in striking that balance. We look forward to hearing your comments and advice so we can move forward expeditiously in implementing this REMS program.

As you will see, the focus of our REMS proposal is on the interface between the prescriber and the patient, and we have outlined goals that are intended to ensure that prescribers make well-informed decisions when prescribing these products, appropriately counsel patients on the proper and safe use of these products, and that patients receive information so that they are informed about the benefits and risks of these products as well as how to use them safely and store them safely in the home so that they are not used intentionally or unintentionally by family members, friends or other household contacts.

As I noted earlier, misuse and abuse of prescription opioids is a societal problem that has

many causes. We recognize that FDA's authority and ability to address all of these causes is limited. Therefore, we plan to continue to partner with other federal agencies, many of whom are represented here today, and stakeholder groups under our Safe Use Initiative to leverage the REMS program that we eventually put in place to help address the causes of misuse and abuse of these products that are beyond FDA's authority and reach.

I would like to thank the members of the committee for your service to FDA as part of this effort. We recognize that it's a sacrifice for each of you to volunteer your time and expertise to advise us on how to assure that we put in place a effective REMS program. We highly value your counsel, and I can assure you that we will listen carefully to the advice you give us today and tomorrow.

Before closing, I'd also like to recognize my many FDA colleagues who have worked on this issue tirelessly over the past year. This work has been on top of their already full schedules, and I know that many have spent countless extra hours beyond their

normal work schedule to help review and address the many differing perspectives on how best to achieve our goals for the REMS program.

You will meet some of the team members today and tomorrow as they make presentations or answer your questions. However, you will not meet all of the members of the team, which numbered more than 80 at last count. So I wanted to take a moment just to recognize their contributions and their dedication to this program. They represent various offices from within the Center for Drug Evaluation and Research as well as offices from the Office of the Commissioner at FDA. So thank you to all of them for their service in this effort.

We'll close there, and thank you again, Mr. Chairman. We look forward to your advice on this issue.

DR. KIRSCH: Thank you. I'll now recognize Dr. Gallagher for his presentation.

DR. GALLAGHER: Good morning. Thanks for inviting me. I'm going to give you a little bit of an overview of what I would call three decades of

experience in managing opioids and the evolution of our experience in medicine and the use of opioids for chronic pain management in hopes of providing you a sense of balance about this issue and maybe where we need to go.

I first want to say that I'm not representing the VA here, the Veterans Administration, although I work there, and happily so, nor any one group. But really, my experience as beginning my career as a family practitioner and then training in psychiatry, and then starting in pain medicine in '82 at the University of Vermont with the help of a NIH grant for training primary care providers in biopsychosocial medicine and finding that 50 percent of our cases were pain cases, the difficult, complex patients and we didn't have much to offer. So I've been immersed in this ever since in a number of different roles.

What I'm going to do is talk about these perspectives. I'm going to review managing versus some pain conditions and risk mitigation in a health system like the VA and others that have data on

disease incidence, prevalence and treatment, and discuss along the way core issues such as the need for standardized patient provider education and training, mentioning a few areas where this has actually been talked about and documented about in some new directives and reports and then talk about the need for balance in policy on opiate analgesia that include not just risk mitigation but also access to good pain care, which is what we really want, to restore quality of life.

So over the last 30 years, there's been a major shift that's occurred in the use of opioids. First of all, in the '70s and '80s, the hospice movement for terminal cancer pain was an important development. When I started practice in the '70s, we didn't have the use of opioids. They were discouraged even for cancer pain management, believe it or not. The VA took up the fifth vital sign in the '90s. JCAHO followed.

Cancer pain specialists in the meantime were documenting that, first of all, cancer pain was under-treated under the leadership of the folks at

Sloan-Kettering, Kathy Foley and Russ Portnoy and their group. And then they were also documenting that long-term follow-up, careful follow-up of cancer pain when in remission or even cured, but patients left with remnants of their cancer or with neuropathic conditions caused by the treatment of cancer did well and were stable over time.

There's also recognition that chronic pain is common, and our epidemiology colleagues started working developing data on how common chronic pain was and how debilitating it was and what a negative impact it had on society. First of all, poorly controlled pain damages the nervous system. We have good neuroscience to document that. Neuroplastic changes are often impossible to reverse. Pain really becomes a chronic disease. There's an interesting paper coming out of the AMA on the term "maldynia," which is pain as a disease, bad pain. Also, documentation from our epidemiology colleagues that pain actually causes depression, anxiety, substance abuse, and now we know it's a risk factor for suicide.

Uncontrolled pain is a chronic public health

problem, and it costs businesses. There's NIH data demonstrating or suggesting that the costs are 210 billion a year, if you lump them all together. But there are costs to businesses of 61 billion a year for what we call presenteeism, inability to work effectively or at your highest level because of pain on the job. And then, of course, there's the cost from taxpayers from Social Security disability, Medicare, Medicaid, workers' comp, et cetera.

In the VA population, which is a well-described population where we have a lot of data, we have the typical aging population of my cohort, the Vietnam cohort, where you not only have remnants of injuries, but you also have the diseases of aging, the multiple diseases of aging that cause chronic, debilitating pain and also are associated with co-morbidities. And then we have what we call the tsunami of incoming injuries from the present war along with, again, additional co-morbidities.

These are some of the more dramatic kind of injuries that we see. But the more common is this composite patient here who is not an actual patient

but a composite of a typical patient we're seeing. There are hundreds of thousands of these coming into the VA right now who have chronic low back pain, minor to major psychological pathology, nothing fixable in terms of surgery but have to be managed and have to be restored to functioning. They may be taking in this case six to eight hydrocodone, acetaminophen, pills daily and have been taking it for many, many months and are dependent on this for getting up and moving around.

There are over 50 percent of new cases coming into the Veterans Administration that have this kind of syndrome of chronic musculoskeletal pain. We have to develop programming in our society, in our communities, to manage this kind of case. But this is representative of many hundreds of thousands, millions of cases outside the Veterans Administration as well.

Years and years of research have established the effects of chronic pain. It's important to recognize that we need to try to prevent these effects from occurring by early and aggressive treatment by what we call a continuum of pain treatment from the

moment of injury to chronicity, so aggressive pain management is important.

There's societal consequences for not doing a good job of taking care of pain, and I've just mentioned them already in terms of healthcare costs, lost workdays. But there's no doubt that chronic pain management needs to be taken very seriously. So while we have the prescription drug abuse issue and the concern about that, an even larger chronic public health problem is pain and its management.

During this time and over the years, it has been demonstrated, effectiveness and safety and tolerability in the use of opioids, but generally speaking, I think it's important to note that these are in structured clinical and experimental settings. A nursing home where patients are given pills on a regular basis to manage their pain, there's been demonstration that they get up more, they have less falls if it's again structured, and they're stronger and they spend more time out of bed and out of chairs when they have their pain managed.

Clinical trials, of course, we have a very

structured approach to providing medications and close follow-up. And then laboratory testing, for example, psychomotor safety testing done in laboratories showing the effects of opioids on coordination, et cetera, these show that, again, structured use in structured settings can show efficacy without risk.

Then there are the documented dangers of alternatives. All of us in pain medicine who have taken care of patients have seen patients overuse and misuse non-opioid analgesics to try to control their pain, often because they're afraid of opioids or they don't have access to them and have GI bleeds which kill, it's estimated, over 15,000 patients yearly from NSAIDs, et cetera. And then the COX-2 issue which people are aware of. And then there's the failure of aggressive treatment such as surgery for back pain. These are alternatives that are dangerous in their own right.

We've also had data now from NIH and others showing that opioids are efficacious in neuropathic pain. And then finally, there's one study out of Hopkins, by Castillo et al, in pain, showing that the

use of opioids was associated at seven years after severe limb injury with a good outcome, not a bad outcome even in patients who had higher pain levels, meaning that probably that it was a proxy for aggressive pain management early in the course. The point is that early intervention, aggressive intervention, including the use of opioids appropriately, is a good idea.

This slide basically is an efficacy comparison of numbers needed to treat neuropathic pain. As you can see, only 2.7 patients were needed to be exposed to opioids in the Roger, et al, study to have a 50 percent impact on their pain. So the point is that opioids are right in there with the other more commonly used medications for being effective in neuropathic pain.

Another health system change, which is related to the way our society allocates resources and trends in medical care, have to do with the evolution and development of managed care. Many of us, including many around the table here and probably in the audience, are aware of the fact that and were

involved in pain rehabilitation systems or programs that actually made a big difference in returning people to work, which was the gold standard back in the ‘80s and ‘90s, and still is really, if you want to talk about restoring quality of life and functionality.

With managed care, the funding for those programs has been cut back, encouraging the use of pharmaceuticals and procedures as short-term gains but without longitudinal outcomes of directed care over a period of time. So there’s a cost shifting in this kind of approach where if patients don’t do well in a system like this, they may lose their job. They may not be able to go to work. In a tight economy, they certainly won’t be able to hold their job in competition with others or get back into the workplace in competition with others. So there’s a cost shifting to us, the taxpayers, who have to fund ER medicine, the public sector, Social Security Disability, et cetera,
and as I mentioned, a drastic reduction in integrated rehabilitation care.

So the primary care provider is caught between a rock and a hard place here. They're mandated to see patients every 10, 15 minutes. These patients are complex, difficult to manage. They haven't had standardized systematic training in pain even though this is the most common thing they deal with in their offices. So they're really in a tight spot, and the usual response is when in doubt, prescribe because it's the easiest thing to do in a setting like that. Medicate first and ask questions later.

Now, this algorithm just is an indicator of how we are now teaching or training providers. It's a guideline of how to take care of pain. And what it suggests is you have to learn how to do the evaluation of the differentiation between the nociceptive and neuropathic pain but also how to evaluate risk all along the way. And it's not just risk for use of opioids. It's the risk for all the different treatments that are listed up here, and these are just pharmacologic treatments. This does not include the very effective co-treatments with behavioral

treatments, self-management training, physical therapy and physical interventions and selective use of pain procedures.

So we need research. Among the millions of patients being treated for pain wouldn't probably care which should be treated with opioids. Patients without addiction or a history of addiction, there are some people who believe that no one should be treated with opioids because of the risk. Obviously, in terms of acute pain, surgical pain, injury pain, et cetera, no one's really saying that. But these are the levels of risk or concern that we need to think about.

Patients with either present or past history of addiction or maybe a predisposition to having difficulty with opioids, such as smoking for example, they deserve pain treatment, too. How do we create programs and structures in our healthcare system to be able to take care of them?

How about pain behavior? Aberrant behavior we call it when they come in early, they call for medications. Are they chemical copers? Are they treating their anxiety, fear? That activates their

pain often because of the way the central nervous system works and actually manages their pain that way or their anxiety that activates pain that way. Are they disorganized or impulsive and just have a hard time getting things together? I'll talk about that some more.

How about depression, low self esteem? These are all factors that come into play when you're trying to look at how to safely and effectively prescribe opioids, and we need that research.

So the policy balance needs to be for quality care to improve the public health problem of chronic pain at lower cost. That means access to effective pain treatment, not handing out pills, but effective pain treatment, and obviously, a routine risk management approach for public and patient safety.

I love these quotes. "The hole and the patch should be commensurate," Thomas Jefferson. "Every reform, however necessary, will by weak minds be carried to excess which will itself need reforming," Samuel Taylor Coleridge.

There's some help on the way. This is a book by Scott Fishman, who many of you know. "Responsible Prescribing," that was published by the Federation of State Medical Practice Boards. Don't forget, every state has its own medical practice board that determines, on top of the DEA regulations, its own regulations and procedures for managing opioids.

Next to it is a new program that's being promoted by the American Pain Foundation. I'm on the board as a disclosure; but to develop a combined program for both patients and providers to help them safely prescribe opioids for pain management. And it's not just about opioids; it's about all the other things that they can do to help with the pain.

The VHA is moving towards a standardized approach with a national pain management directive and strategy. And we have an office. We're the first federal program to really have an official office under Bob Kerns' direction. The DoD and VA chronic opioid therapy guidelines are out now. They're building on what was developed by the American Pain Society, American Academy of Pain Medicine clinical

practice guidelines. These are very specific, and we're hoping to add clinical teaching or training programs and modules to them.

Then the VA is working on a national opioid pain care agreement to standardize things. And just to remind you that, again, we're talking about a tiered approach so that in the medical home model of patient care, self-management and training in self-management is very important and education. But then you go up the line to increase the intensity and complexity of care, depending on the situation.

So what works in educating providers in opioid management and analgesia management and risk management? Well, we need to measure effectiveness in terms of clinical practice change. We want to see if appropriate use of opioids occurs within a biopsychosocial paradigm that focuses on patient outcomes. That's the key, pain control, not in the service of just pain control, but in functional outcomes and improvement of the quality of life of this individual.

Also, risk management procedures need to be

instituted because of the very real risk that we're here to address in the next two days. So there are routine opioid pain care agreements that are now being advised for the VA and other systems. Practice audits to identify outliers and to review those cases are another approach to this.

What works to change practice? Well, we know that CME seminars, reading, they may work for some, but do they actually change practice? Well, there's some evidence that they might. We don't know how long term that is. But we do know what does work. Residency training, apprenticeship model of residency training works very well to ingrain systematic approaches to disease management in a number of different diseases. We need good programs, training programs, for residency.

The AMA Summit, which was held last fall, the report is finally out, and it strongly recommends that we develop standards for every residency program in pain management no matter which residency it is and also pain medicine training and training programs in every medical school for training medical students and

pain fellows as well.

Academic detailing is something that works in a postgraduate setting. The ECHO rural education program in the Southwest is very effective using telemedicine, using return visits, lectures and sort of almost apprenticeship model at a distance.

Then finally, systems support for case management is another important part where the provider is not sort of alone in an office with a patient but part of a structure that provides case management support, and there's very good evidence that changes practice.

These are the principles of academic detailing. It's important to have face-to-face sessions. This reminds me back again to my NIH grant back in the late '70s, early '80s when I traveled around Vermont to primary care offices, meeting with them on a monthly basis to go over tough cases, and over a four-year period improving their skills so their skills in integrating psychiatry and primary care were elevated.

These programs now are being evaluated very

systematically and showing real impact on elevating the skills of primary care providers in rural settings in developing good skills in pain management. So it's a longitudinal apprenticeship relationship over time.

Here's another example. These are data from the medical examiner database in Utah where you can see a drop in the number of opioid-related overdose deaths in 2008 from a high of 317 in 2007. And this is a program, another academic-detailing program, that was run by Health Insight. And you can go to their website and look up the details of this. But again, the same principles were used, and some of the outcomes are in your slide set that I'm not going to show.

Opioid renewal clinic, another approach, where a primary care provider, a nurse practitioner with no special expertise in pain, on instruction from her hospital basically developed a systematic approach to training providers in primary care how to get urine, order your drug screens and do opioid treatment agreements and then developed a pharmacy pain clinic that actually did renewals with systematic review of

risk and functionality and outcomes. I'm not going to go through this. It's in your slide set or you can look at the paper in "Pain Medicine."

The point is that it was very effective. I'm going to show you just some of the efficacy data, the effectiveness data, over time. Out of 784 referrals in a three-year period, 47 percent were for aberrant behavior and 53 for nonaberrant behavior but they were at risk. There's 100 percent adherence for those at risk who had these kinds of problems.

But what's interesting is the aberrant behavior patients who, generally speaking, would not be provided opioids because they were not taking them the right way or coming in early or going to the ER or whatever, for that group, 40 percent of them settled right down with a good structured case management approach and got the appropriate treatment that they needed, and then 51 percent were discharged. So at least in this case, a structured case management approach with a organized system of care provided at least 40 percent of these cases with opiate analgesic when they needed it rather than not giving them

treatment at all. So this is a promising-type approach that can be used as case management.

Another is Jodie Trafton's approach at Stanford, and the VA at Palo Alto, where she again is developing a system support on the computer for guiding providers through managing opioids and managing risk in opioids.

Where are we with the opioid pain care agreements? I like my way or the highway because they've been misused. If someone screws up, has a little bit of aberrant behavior, there's an excuse for discharging them. That's not the way things are, at least in the VA, where we take responsibility for our patients longitudinally and must take care of them no matter what.

There's a lot of difference in one opioid agreement and another, and there's lack of standardization. So you can imagine going from one health system to another in our traveling population moving, or mobile population even within the VA or outside the VA and having difficulty in following this.

This slide basically shows the evolution of the opioid treatment agreement group which involved a number of different professionals from legal, ethics and all specialties and all disciplines in healthcare. The point is it took a long time, but we're almost there.

The balance between patient's rights, public safety and clinical judgment and responsibilities has to be involved in any opioid treatment agreement and any opioid management program. So obviously, access to quality of care, confidentiality and safety are important. Public safety is important. But we have to also recognize that the clinician has the ultimate responsibility for making judgments clinically, and we have to provide the support, the education and training that allow them to do a good job.

In my experience and the experience of many of those in this room, if providers have the right training, they like taking care of pain patients because it has such a huge impact on their lives, a positive impact if it's done well and effectively.

So a step care model, this is a complex

slide. I'm not going to go through it all, but the point of this slide is that you can develop a systematic approach to providing integrated risk approach, risk management and pain treatment, in primary care if you have the right tools and system supports. But you have to integrate behavioral medicine. You have to integrate the access to control or case management opioid prescribing within chronic pain management. And then you have to have access to effective pain medicine and complex care in pain medicine for support and for developing the algorithms within your own health system to take care of patients and also mental health specialty programs.

Finally, for those who get to the point where they're disabled and require rehabilitation, we must access -- there are only a few rehabilitation programs left in the United States really. Some of them are here in the room. And it's a shame. We need to make those programs in access.

So in summary, we must address the core problems. We need systematic standardized education and training for all providers supported by well-

trained, accessible pain medicine specialists and addictionologists. We have to develop system redesign. The medical model is a step forward in that regard so that we can have the resources upfront of quality of care to prevent chronicity. And we must balance risk control with access to quality care in making policy. Thank you very much.

Comments and questions?

DR. KIRSCH: Thank you.

So for the members of the committee, if you have questions, please raise your hand, and we'll keep a tally up here at the head of the table and call on you when it's your turn.

Dr. Bickel?

DR. BICKEL: Thank you for that very interesting and comprehensive presentation.

Could you reflect on your personal experiences with reflect to diversion from medications provided through the VA?

DR. GALLAGHER: It's interesting because one doesn't get too much information about diversion when one is working in the VA as a clinician. In other

words, one doesn't really know about diversion when it occurs because there's a lack of connection about that.

There's suggestion certainly from our data in the Philadelphia VA that patients who don't want to comply with the structured approach, that would certainly suggest, for example, that maybe some diversion is going on.

DR. KIRSCH: Dr. Denisco.

Oh, I'm sorry. Dr. Krantz?

DR. KRANTZ: Dr. Gallagher, just a quick question. You mentioned some of the issues around the societal consequences, but I didn't see any references. I was wondering, is there data regarding decrease in terms of disability, decreased government dependency on programs like Medicare and Medicaid that you alluded to or increases in employment? And the reason I say that, those are more distal public health consequences that we could really say that the long-acting opioids are providing a benefit. We saw a similar model when we used opioids for treating those with addiction where their societal things would kind

of get better. So I was just wondering if there's any data on that.

DR. GALLAGHER: Data on the effects of long-acting opioids and improving outcomes; is that what you said?

DR. KRANTZ: Yes, you have the slide that talked about the societal consequences, healthcare cost, disability, lost workdays, business failures, higher taxes. And I wonder what the data would be. I know the data in the methadone area where I used to work, but I wonder what would that be in the chronic pain arena for the opioids.

DR. GALLAGHER: We don't have good data showing the effects of being on opioids long term for improving those kinds of data, those kinds of public health outcomes. However, my own personal experience, having run a pain rehabilitation program -- and I'm sure those here in the room, some of you around the table, have had this experience, where opioids judiciously used can help a patient respond well to a rehabilitation program, get through painful physical therapy and get back to work because they have

opioids. So opioid availability is key to success in some of those programs for a certain percentage of patients.

DR. KIRSCH: Are there any other --

Dr. Kosten.

DR. KOSTEN: Just a brief question. There are bills before Congress now for these centralized -- I mean, a number of states have them on prescribing and keep track of who's getting what kinds of medications, and, therefore, looking for abusing patients. The VA, of course, has a centralized pharmacy database where one can go through what medications people are getting from potentially multiple prescribers.

Are there data from those databases yet to see if that works in this system? And I realize people could go outside the VA to get their multiple prescriptions. But even within the VA system, is there data on that you could comment on?

DR. GALLAGHER: Yes, this is a very important problem or issue because each state has its own regulations so there are 50 different regulations,

and there's one VA. And we're working hard to develop a way to work together with prescription monitoring programs between the VA and the states. It's an important issue because it allows us to have more comprehensive information about how medications are being used.

I mentioned in one slide the opioid high alert program which identifies in our databases patients who are taking very high doses and enables or facilitates a review of those cases in facilities. And that's one kind of effort where you could actually see some good results.

DR. KIRSCH: Dr. Hatsukami?

DR. HATSUKAMI: I have two quick questions. One of them is, at the VA, your standardized provider education and training, is that mandatory or is that on a voluntary basis?

DR. GALLAGHER: Well, it's being strongly encouraged. That's my personal opinion, but I think it's probably true. And what I'm saying is there's a new directive from the VA that strongly encourage facilities to do more education.

DR. HATSUKAMI: And is there any data in terms of the percent of people that actually do engage in this type of training?

DR. GALLAGHER: I don't have those data myself.

DR. HATSUKAMI: Okay. And just one other question.

You do talk about the continuum of step care, and it does look like an ideal program. But what about the rural areas? What about areas that don't necessary have these resources?

DR. GALLAGHER: Well, that's an interesting question. The VA and the DoD now are addressing that. The ECHO program in the southwest is a great example. The academic detailing slide is a program that does telemedicine seminars out in the rural sites, sort of the traveling expert kind of thing to elevate the skills of the primary care providers in a particular area. They show very good data, for example, in Hepatitis C infections where there's a big delta between those who don't get it and those who do get the academic detailing. They use a lot of

telemedicine, and those are things that we're going to be using.

The Northwest, the Seattle University of Washington contact, which includes a lot of states in the Northwest, including Alaska, that are quite rural and quite distant, scattered populations, are using those kinds of technology very effectively and have been for years.

DR. KIRSCH: Thank you.

Before we go on to our next speaker, I'd like to recognize Dr. Denisco to introduce himself as he came in a bit late.

DR. DENISCO: I apologize to the Chair for that and colleagues. Richard Denisco from the NIH, specifically NIDA, and the Department of Epidemiology Services and Prevention Research. Thank you.

DR. KIRSCH: Thank you.

Our next speaker is Dr. Laura Governale.

DR. GOVERNALE: Good morning. My name is Laura Governale from the Division of Epidemiology in the Office of Surveillance and Epidemiology. Today I will be presenting the outpatient drug utilization

trends for opioid drug products in the U.S. from years 2000 to 2009.

The following is an outline of my presentation. First, I will go into the distribution of immediate-release and extended-release long-acting opioids to determine where these products are being primarily used. Then I will describe the prescription and patient trends and characteristics and go into prescribing specialties as well as diagnoses associated with the use of these products. And finally, I will present the limitations of my analysis and conclude with a summary of my presentation.

For this analysis, opioids were grouped into the following categories. Extended-release and long-acting opioids, which all belong in the Schedule II class include oxycodone, morphine, fentanyl transdermal, hydromorphone, oxymorphone and methadone. Immediate-release opioids were broken down into the following categories.

I'm not going to read through all of the individual ingredients, but they were based on formulation and scheduling classification. Single-

ingredient Schedule II opioids, combination Schedule II opioids; single-ingredient Schedule III and IV opioids, combination Schedule III and IV opioids; hydrocodone, which belongs in Schedule III; and buprenorphine, which belong in Schedule II.

For the remainder of my presentation, I will be referring to the extended-release and long-acting opioids as extended-release opioids.

We looked at the distribution settings of extended release and immediate release opioids to see where they were primarily being used. Extended-release opioids are primarily used in the outpatient retail pharmacy setting and accounted for approximately 76 percent of sales distribution in year 2009. Immediate-release single ingredient and combination opioid products were also distributed primarily to the outpatient setting with roughly 60 percent or more of sales going towards the setting of care. However, single-ingredient morphine and combination codeine products were primarily distributed to nonretail settings of care such as inpatient hospitals.

Next, I will describe the prescription and patient utilization trends and characteristics. For this analysis, we used the national prescription dispensing data from the SDI Vector One national.

SDI is a national level prescription and patient tracking service. It receives over 2 billion prescription claims per year and represents over 160 million unique patients. The number of dispensed prescriptions is obtained from approximately 59,000 pharmacies in this country and accounts for nearly all retail pharmacies and approximately half of all retail dispensed prescriptions nationwide. The pharmacies in the sample include national retail chains, mass merchandisers, pharmacy benefit managers and their data systems and provider groups.

This slide shows the share of outpatient opioid dispensed prescriptions for the entire market of prescriptions for year 2009. So in year 2009, approximately 3.6 billion prescriptions were dispensed from outpatient retail pharmacies. And of these, 7 percent, or approximately 257 million prescriptions, were opioids. Breaking that down further, immediate-

release opioids accounted for about 91 percent of all opioids, and extended-release opioids accounted for about 9 percent of all opioids in year 2009.

This chart shows the trend of the dispensed prescriptions for extended-release and immediate-release opioids for year 2000 to year 2009. So for the immediate-release opioids shown in the blue bar here, the immediate-release opioids increase from approximately 165 million prescriptions to approximately 234 million prescriptions in year 2009. And that was about a 42 percent increase over the time period.

For the extended-release opioids shown in the purple bar down in the bottom, they accounted for approximately 9.3 million prescriptions in year 2000 and increased by 146 percent to about 22.9 million prescriptions in year 2009.

This chart breaks down the extended-release opioids into the various active ingredients. The pink line above is represented by oxycodone, and it accounted for the largest share of the market over the 10-year period. And in year 2009, oxycodone accounted

for approximately 34 percent of the extended-release market or about 7.7 million prescriptions. Following that was the fentanyl transdermal, which accounted for about 22 percent of the market shown in the light blue bar line at the top or approximately 5.1 million prescriptions. The darker blue triangle line you can see is represented by extended-release morphine, which also accounted for about 22 percent of the market or approximately 5 million prescriptions. And the purple line represented by methadone accounted for about 19 percent of the market or about 4.4 million prescriptions. And finally, oxymorphone accounted for only 3 percent of the market or about 550,000 prescriptions in year 2009.

This chart shows the breakdown of immediate-release opioids from year 2000 to 2009. And again, the pink line above represents hydrocodone products. And hydrocodone accounted for approximately 123 million prescriptions in year 2009 or about 53 percent of the immediate-release market. The combination Schedule III and IV opioids shown by the blue triangle bars accounted for about 14 percent of the immediate-

release market or about 33.3 million prescriptions.

The combination Schedule II opioids shown in the lighter shaded blue line also accounted for about 14 percent of the market or about 32.6 million prescriptions. And for the single-ingredient Schedule III to IV opioids shown in a purple line, accounted for about 11 percent of the immediate-release market or about 25.5 million prescriptions. And the single-ingredient Schedule II prescriptions accounted for about 6 percent of the immediate-release market or about 13.7 million prescriptions. And finally, buprenorphine products accounted for about 2 percent of the market or about 5.7 million prescriptions in year 2009.

We also looked at the mean days of therapy per dispensed opioids prescriptions from year 2000 to 2009. This analysis was used as a proxy for a duration of use analysis, but it's not a duration of use analysis. So for extended-release opioids, they had the greatest mean therapy days per prescription, and it ranged from 23 to 28 days over this 10-year period. For immediate-release single-ingredient

opioids, the therapy days per prescription ranged from 13 to 21 days, and the immediate-release combination hydrocodone and buprenorphine products ranged in about 8 to 14 days per prescription.

This table shows the percent of total prescriptions dispensed as new, continuing or switch/add-on type prescriptions for immediate-release and extended-release opioid products for year 2009. This represents those patients who had not had an opioid product dispensed to them in the previous one-month period.

So for immediate-release opioids, we see that approximately 40 percent of prescriptions dispensed to these patients had not had a opioid product dispensed to them in the previous month. For the immediate-release opioids, about a quarter or slightly over a quarter of prescriptions were dispensed to patients who had not had a previous opioid prescription in a previous month.

This graph, we're actually looking at the number of unique patients who received an extended-release opioid product from years 2000 to 2009. And

similar to dispensed prescription data, the number of patients also increased over this time period from approximately 2.7 million patients in year 2002 to a peak of 3.95 patients in year 2008, and then it slightly decreased to about 3.8 million patients in year 2009.

Here, we're breaking down the number of patients on extended-release opiates by age and sex, and we see that the age 50 to 59 category accounted for the largest proportion of use with about 27 percent of patients. The age 40 to 49 category accounted for 22 percent of extended-release patients, and the age 60 to 69 category accounted for about 17 percent of use. Patients aged 0 to 19 years old accounted for less than 1 percent of total extended-release opioid use during year 2009. And in general, the females had a slight majority in use in extended-release opiates.

Next, I'm going to switch gears a little bit and describe the prescribing specialties and diagnoses associated with use of these products.

In this graph, I'm showing the number of

prescriptions dispensed in the U.S. for the immediate-release and extended-release opiates by the top 10 prescribing specialties. In general, the prescribers for immediate-release and extended-release opioids were similar. For instance, among the top two prescribers for immediate release and extended release opioids were general practice, family medicine and doctor of osteopathy, followed by internal medicine specialties.

Among the immediate-release opioids, the number three prescribers were dentists which accounted for about 8 percent of immediate-release prescriptions or about 18 million prescriptions. And the other notable difference with the immediate-release prescriber was emergency medicine specialty, which accounted for about 5 percent of immediate-release prescriptions or about 11 million prescriptions in year 2009.

Moving back to the extended-release prescriber side, the differences we see here are the neurologists and the hematology specialty which accounted for about 3 percent and 2 percent of

prescribing for extended-release opioids.

Moving on, I'm going to be describing the diagnoses associated with the use of these immediate-release and extended-release opioid products. And for this analysis, we used the SDI Physician Drug and Diagnosis Audit. And this is a office-based physician survey data which is composed of approximately 3,200 office-based physicians that monitor disease states and physician-intended prescribing habits on a national level. This survey is designed to provide descriptive information on the patterns and treatment on diseases in the country, and it represents approximately 30 specialties across the country and includes about 115 pain specialists in each monthly survey.

So this slide shows the diagnoses associated with the use of immediate-release and extended-release opioids for year 2009. We group the ICD-9 codes into the following categories, and the most common use for both immediate-release and extended-release opioids were conditions related to diseases of the musculoskeletal system and connective tissue. And we

can see that for the immediate-release side, it accounted about 30 percent of uses, and for the extended-release side, it accounted for about 56 percent of uses.

The second most common use for immediate-release opioid products were conditions related to fractures, sprains, contusions and injuries and accounted for about 23 percent of uses, whereas on the extended-release side, it only accounted for about 6 percent of uses.

For the extended-release opioid products, the second most common use or condition related to headaches and nerve pain shown by the orange slide here, it accounted for about 14 percent of uses. And the third most common diagnosis were related to neoplasms and cancer pain, which accounted for about 11 percent of uses.

Another measure we looked at with this survey database was the reason for switching to an extended-release opioid product. The universe of pain product we were looking at included both narcotic and non-narcotic pain products. So with that said, the

most common reason why a physician would switch a patient to a pain product to an extended-release opioid product was due to ineffectiveness.

So before I conclude, I want to present some of the limitations of my analysis. In this analysis, we only looked at outpatient opioid use. Therefore, we could not see use in the inpatient side or the emergency department side or any other non-outpatient settings. We were also unable to assess chronic versus acute pain using ICD-9 codes alone. And also, we could not determine opioid tolerance without doing a longitudinal-patient-level analysis that encompassed a wider range of settings of care.

So in summary, approximately 3.8 million patients annually received an extended-release opioid product in the outpatient setting. And about half of the prescriptions for extended-release opioids were prescribed by primary care practitioners. The data also suggests that about a quarter or more of patients on extended-release opioids have not had a opioid prescription in the previous month so that they're receiving it for the first time. And extended-release

opioids were more commonly used for conditions related to chronic pain such as back pain and arthritis. And finally, extended-release opioids had a longer mean days of therapy per prescription than immediate-release opioids. Thank you.

DR. KIRSCH: Thank you.

Dr. Dormitzer?

DR. DORMITZER: Good morning. My name is Cathy Dormitzer. I'm an epidemiologist in the Division of Epidemiology in the Office of Surveillance and Epidemiology.

Today I will present a brief background on the National Survey on Drug Use and Health and on the Drug Abuse Warning Network. I will present some initial findings from both data sources, and then I will discuss the methods used to calculate estimates of drug abuse ratios. I'll present the estimates themselves and then a summary and conclusions drawn from these data.

I will start by presenting findings that have already been published from the National Survey on Drug Use and Health, which is also called the NSDUH

or Nizda (ph). It was formerly called the National Household Survey on Drug Abuse, and it measures prevalence and correlates of drug use in the United States.

Information is provided on the use of illicit drugs, and that includes the nonmedical use of prescription drugs as well as use of alcohol and tobacco among members of the United States households age 12 and older. Questions include age of first use as well as lifetime, annual and past month usage for the following drug classes: Illegal drugs, such as marijuana, cocaine, hallucinogens, heroin, et cetera, and the nonmedical use of prescription drugs, including pain relievers, which are opiates, tranquilizer, stimulants and sedatives. Date of first use is collected as well as symptoms of dependence and abuse.

Except for OxyContin, only lifetime use for a specific drug substance is collected. It does, however, provide information on opioid analgesics as the category pain relievers.

Nonmedical use is defined as taking

prescription drug that was not prescribed to the respondent or taking the drug just for the experience it caused. And after responding positively to having taken a pain reliever nonmedically in their lifetime, this is the pill show card that is given to the respondents to assist them to identify the drug substance they've used.

The proportion of the U.S. population age 12 and older that has used a pain reliever nonmedically has increased over the years. According to the data collected in 2008, more than 13 percent of the population had used a pain reliever nonmedically at least once in their lifetime. And roughly 2.2 million Americans age 12 older initiated using pain relievers nonmedically in 2005. And that number of initiates has remained stable through 2008.

This is a pictorial representation of how respondents reported the source of the pain reliever that was taken nonmedically. As you can see, 20 percent of them obtained it from one doctor, and 70 percent obtained their pain reliever from a friend or relative, either for free or because they bought it.

And among the relatives, 80 percent obtained the pain reliever from one doctor. Very little was obtained from the Internet, and a low proportion was obtained from more than one doctor.

The Drug Abuse Warning Network is a public health surveillance system that's administered by SAMHSA. Data are collected on a nationally-representative, multi-stage probability sample of hospitals. Detailed information on drug-related emergency room visits are collected, and it provides national estimates on these visits.

National estimates for a variety of opioid analgesics were requested from SAMHSA. Estimates were requested for extended-release long-acting opiates as well as the immediate-release opiates. Not all opiates requested are included in this final analysis. If the relative standard error is greater than 50, the estimates are suppressed because there is too much imprecision in the estimate.

The relative standard error is expressed as a percent of the estimate. So 50 means that it's 50 percent of the estimate. And since the confidence

interval is plus or minus two standard errors, that means that the confidence interval is as large as the estimate itself. So national estimates were not provided for oxymorphone or for fentanyl transmucosal products because the RSE was greater than 50.

To understand how DAWN ED visits are related to drug misuse and abuse, SAMHSA developed two constructs based on the type of case of the emergency room visit. First, there are cases related to the nonmedical use of pharmaceuticals otherwise known as NMUP. These are ED visits that were classified as overmedication, in other words, exceeded the prescribed dose, and the case type other, which generally has been sued to classify drug abuse cases.

There are cases related to all misuse and abuse, which is called ALLMA. These are the ED visits that include NMUP but also include ED visits where illegal drugs or alcohol was present, and these cases are called ALLMA or all misuse and abuse.

So DAWN can provide estimates on the nonmedical use of opioids, but it does not provide information on drug exposure or availability of drug

utilization. And so prescription drug utilization is used as a proxy for drug availability or exposure.

As you will recall from Dr. Governale's presentation, there are large differences in how different drug substances have been prescribed. So the drug abuse ratios take these differences into account when calculating drug abuse ratios. DAWN data, estimates, are used as a numerator, and drug utilization is used as the denominator to estimate abuse ratios for both the nonmedical use of pharmaceuticals, NMUP, and all misuse and abuse, ALLMA.

Now, here are the national estimates of the nonmedical use of pharmaceuticals from 2004 to 2008. As you can see, the national estimates for ED visits related to hydrocodone were higher than for other drug substances. There were almost 40,000 NMUP visits with hydrocodone in 2004, and those rose to 89,000 ED visits in 2008.

For immediate-release oxycodone, there were more than 26,000 ED visits in 2004 and 66,000 ED visits in 2008. For extended-release oxycodone, there

were 26,000 ED visits in 2004 and 66,000 visits in 2008. Actually, not exactly, but -- okay. For methadone, there were almost 36,000 ED visits in 2004 and more than 63,000 visits in 2008. For fentanyl transdermal products, there were 97,000 in 2004 and 20,000 in 2008. And for morphine extended-release, the estimates range from 4,700 to 5,700.

Here are the ALLMA ED visits, and as you can see, they are higher, and that's because it includes all the NMUP visits plus ED visits where alcohol or an illegal drug was also associated with that same visit.

This is a summary of the number of ED visits associated with the nonmedical use of pharmaceuticals per 10,000 prescriptions. And as you can see, the NMUP ratios for immediate-release products are lower than the ratios found for the extended-release formulations. And all these ratios for each drug substance have gone up from 2004 to 2008. And this was also found for the ALLMA ratios. As you can see, all ratios for each drug substance has gone up from 2004 to 2008.

As you may have noticed in the previous

slides, I did not present NMUP and ALLMA ratios for methadone. The slides of ED visits show that the number of visits related to methadone ranged from 40,000 in 2004 to 70,000 in 2008. And the only extended-release drug that was higher was for oxycodone. But the difficulty is that the same methadone products are used both as an analgesic product and in opioid-dependence treatment programs, or OTPs, and we do not have data on the amount of drugs dispensed in OTPs. So as a result, the numerator, ED visits, includes patients that either took methadone for analgesic purposes as well as that was received in OTPs. And the denominator only includes analgesic methadone. So it would be a larger numerator over a smaller denominator and that would inflate the ratios. So that was why they were not presented, because it wasn't reliable.

When examining these ratios, it is important to keep in mind the limitation. These data are in no way linked, drug utilization and DAWN. And there is no information provided by DAWN on how many patients had a prescription or if a member of their household

had a prescription to the drug that resulted in the ED visit, and that's an important limitation.

The sampling methodologies used to derive the national estimates are in no way linked or connected, and, thus, the confidence intervals for each estimate are different. And so we cannot compute confidence intervals for these ratios. The populations are similar because it's the United States, but DAWN is the population of emergency rooms, and drug utilization, the population is retail pharmacies. Lastly, when estimates are small, it is generally expected that it's not going to be as precise of an estimate as when estimates are large.

At the same time, the results found between the proportion of NMUP and ALLMA and the ratios are consistent. Although in absolute numbers, the public health burden for extended-release opioids appear lower, the number of ED visits per 10,000 prescriptions for extended-release products is higher.

As previously presented, a large proportion of Americans age 12 and older, 13 percent, have used a pain reliever nonmedically at least once in their

lifetime. And more than 2 million Americans are initiating use of a pain reliever each year, and that rate has been consistent for over the past five years. Most have obtained the pain reliever from one doctor.

So the data are consistent between NSDUH and DAWN, and both indicate the nonmedical use of opioids continue to be an important public health problem.

DR. KIRSCH: Thank you.

The next speaker is Dr. Conway.

DR. CONWAY: Good morning. My name is Kevin Conway. I'm here on behalf of the National Institute on Drug Abuse. I'm the deputy director of the Division of Epidemiology Services and Prevention Research there. Our prospective in this division is one that focuses primarily on public health. We're sort of the public health lens for the National Institute on Drug Abuse. And today, I'll be talking about prescription opiate abuse from two different large data sources, the Monitoring the Future study and the Community Epidemiology Work Group.

These two data sources provide us with slightly different perspectives on prescription drug

abuse in general and opiate abuse in particular. National trends are provided through the Monitoring the Future study, and much more local trends are provided through the Community Epidemiology Work Group.

By way of background, the Monitoring the Future study is an annual school survey conducted by the University of Michigan through a grant from the National Institute on Drug Abuse. This study has been going on for 12th graders since 1975, and in 1991, 8th and 10th graders were added to the sample.

In 2009 -- and these are data that I will be showing you -- there were approximately 46,000 students representing a nationally-representative sample of nearly 400 public and private schools in the United States. Questionnaires were administered to students in their classroom during the spring term.

The 2009 MTF sample, as I said, comprises approximately 46,000 students, about 16,000 from 8th grade, 16,000 from 10th grade and about 14,000 from 12th grade. The response rates for each of these different cohorts ranges from 82 to 89 percent. And

the number of schools in each of these subgroups ranges from 119 to 145, so it's a fairly large representative sample of students in the U.S.

So the bottom line from the MTF 2009 data is very similar to what we saw in 2008. Rates of prescription drug abuse remain alarmingly high, and it's driven predominantly by the misuse of opiate analgesics.

In the 2009 Monitoring the Future study, here this slide shows the prevalence of past-year drug use among 12th graders. So these are 12th graders, or seniors, who reported having used any one of these drugs listed in the past year. And not surprisingly, alcohol and marijuana are the most commonly reported drugs used. But it might surprise you that all these listed in yellow are prescription drug drugs. These are used at alarmingly high rates among high schoolers in this country. And two of the top 10 happen to be opiate analgesics; 9.7 percent of 12th graders in 2009 reported using Vicodin in the past year, and almost 5 percent reported using OxyContin in the past year.

In terms of trends, so looking at rates as

they may or may not change over time, it sort of gives us a perspective of the shifting landscape of drug use historically. So here I'm presenting data from 1991 through 2009 showing, just for perspective and comparison purposes, percent of students reporting any illicit drug use in the past year. And as you can see, the rates begin in 1991, around 30 percent for 12th graders, and increase to about 38 or 39 percent in 2009.

You see generally that for all grades, the rates increase from '91 to about 1999 or so and slowly decrease thereafter. In almost all cases, rates of 12th graders exceed those of 10th graders, which in turn exceed those of 8th graders. There are some exceptions to that, however.

Here I'm focusing in on the percent of students reporting nonmedical use of OxyContin in the past year by grade. In 2009, as I said, roughly 5 percent of both 10th and 12th graders report using OxyContin in the past year, and the rates are still surprisingly high among 8th graders. So if you look at the trend here from 2002 to 2009, especially for

12th and 10th graders, it appears to be an increasing trend line. We don't see any differences that are reliably different between 2008 and 2009, however.

Here's the same slide for Vicodin. Pretty stable rates from 2002 to 2009 for all grades, hovering around 10 percent for 12th graders, around 6 or 7 or 8 percent for 10th graders, and right around 2 or 3 percent for 8th graders. Again, we don't see any significant differences between '08 and '09 data.

Like you just saw from the National Household Survey of Drug Use and Health, we in the MTF study asked students where they got prescription drug use should they have reported using them in the past year. And this shows in percent, in nonmutally exclusive categories, that 51 percent, or roughly 52 percent, were given the prescription drug from a relative, nearly 34 percent reported having bought the drug from a friend or relative, and 30 percent received it from a prescription. So in three major categories here, friends or relatives are the primary source for receiving prescription drugs.

Shifting gears a bit to the Community

Epidemiology Work Group, this is a public health drug abuse surveillance system established in 1976. It's really a network of different sites across the United States that try to give us a more micro view of what's going on in local metropolitan areas. It sort of gives us a heads-up or tells of potential new trends in drug abuse. The sites are distributed across the U.S., including Honolulu, and like Texas, they do everything big, so the whole state is a site.

The bottom line for CEWG is availability, misuse, and consequences of opiate analgesics continue to rise. These are not new data. Primarily, I'll be showing you data that were presented at the meeting in January of 2010. These data come from 2009, and they represent data from the ARCOS, which is a way of tracking pharmaceuticals as they move from the manufacturer to pharmacies.

What you see here for the United States in the lower line, as well as for this particular reporting site in Arizona, you can see the slope of the curve is very high starting in the first quarter of '97 and increasing pretty linearly upwards through

2006.

In terms of consequences of use of opiate analgesics, here this slide shows poison control reports from the city of Detroit from the time period of 2000 through 2008, according to different particular drugs, oxycodone, hydrocodone and methadone. And clearly, out pacing all the others in terms of poison controls, and increasingly so from 2002 to 2008, are poison control calls due to hydrocodone, increasing from approximately 251 in 2002 to 568 in 2008.

This slide, also from the greater Detroit area in Wayne County reporting the number of deaths with laboratory confirmed presence of various opiates, fentanyl, hydrocodone, oxycodone and methadone. The line on top, the grayish line which shows the steepest increase, almost linear, is hydrocodone, steadily increasing. But all of these trends are showing linear increases over time, but the most dramatic one is for hydrocodone.

There’s also considerable spike in 2006 for fentanyl due to what is believed to be a bad batch of

fentanyl coming through Mexico and causing a sudden outbreak of overdoses. That is correct data. That's not an anomaly.

Here tells a slightly different story. The number of other opiates that -- so it's a non-heroin-related treatment admissions to non-crisis services in various regions in New York City and surrounding. And the top two bars in the purple and the light blue represent the suburbs in upstate New York. The point of this slide is to show that although heroin continues to be a major source of concern within New York City in terms of consequences, the story for the New York suburbs, Long Island and upstate New York is for the non-heroin opioids.

So the top two lines, the top line is the purple line which is upstate New York. New York suburbs is in light blue. Upstate New York is the one in the middle, and the lowest one in orange in New York City. So treatment admissions is really increasing dramatically in the suburban areas of New York City.

In the Twin Cities in Minnesota, here

treatment admissions for opiates other than heroin have surpassed those of heroin itself in the quarter beginning 2008. And from a law enforcement perspective, here from a CEW site in Maine, the pharmaceutical narcotics are increasingly demanding the attention of law enforcement here reflected in the percentages of arrest from 2003 to 2009.

More information about prescription drug abuse, the research that we do and the interventions and treatment that we provide is available at our website, www.drugabuse.gov. Thank you.

DR. KIRSCH: Thank you.

We have a few minutes for questions.

Any of the committee members have questions?

Dr. Beardsley?

DR. BEARDSLEY: I'd like to ask Dr. Dormitzer a question regarding the percentile increase from 2004 to 2008 in emergency room visits with regards to the extended-release products versus the immediate-release products. It appears that there was a greater percentile increase in the extended-release products versus the immediate-release products but

that difference didn't appear dramatic.

Was there a statistically significant percentile increase in the extended-release products with regards to emergency room visits versus the immediate-release products during that period of time?

DR. DORMITZER: It depends on the drug substance itself. For some, the increases were not statistically significant from one year to the next, but from 2004 to 2008, the increases were significant. But comparing between the two, we didn't -- I'm not sure how we would do that.

DR. BEARDSLEY: I guess what I'm getting at is should we be more concerned about the extended-release products versus the immediate-release products at least given the emergency room data that you showed us?

DR. DORMITZER: Yes. Basically what we've seen is, if you were to look at a graph, the emergency room visits are increasing almost parallel to the same slope as the drug utilization. In other words, as prescriptions increase, so do emergency room visits, but they're not completely parallel because otherwise

you should see that they would just fall lockstep. What you're seeing is that emergency room visits are increasing at a slightly faster pace than prescriptions, if that's making any sense.

DR. BEARDSLEY: I think so. How about if I just get to the bottom line?

DR. DORMITZER: Yes.

DR. BEARDSLEY: Given your data, should we be more concerned about extended-release products versus immediate-release products, given the data that you showed us today?

DR. DORMITZER: The data is showing higher ratios of number of emergency room visits per 10,000 prescriptions for the long-acting extended-release products, yes. If you look at the table of NMUP and ALLMA, the extended-release products are resulting in more emergency room visits per 10,000 prescriptions. So less utilization, less emergency room visits. So if a drug isn't sold, then people aren't going to the emergency room for it.

DR. KIRSCH: Dr. Farrar, move on to the next question.

DR. FARRAR: Question for Dr. Conway.

In the first set of slides, which showed the drugs that were abused by high school students, you pointed out that Vicodin and OxyContin were two of the major drugs there. Sort of back of the envelope recalculation of some of the numbers here, understanding that they're not unique, that the categories are not unique, it seemed to indicate, at least to me, that the amount of opioid abused was in approximately the same range as stimulants and sedatives and hallucinogens, not including marijuana, obviously, which is the highest.

I wondered if you'd looked at the growth or the trends over time for some of the other categories and might inform us about the rates of opioid misuse/abuse versus some of the others.

DR. CONWAY: Yes, so when compared to the broad class of any drug use, any illicit drug use, it's fairly flat over time, right. But when you contrast that to specific opiate analgesics, more recently, we've seen that students are using opiate analgesics more so than they used to and the rates

over time have increased more readily relative to other drugs. So it's a growing problem that hasn't changed in very recent years. It started growing several years ago and remains concerningly high.

DR. FARRAR: So just to clarify, the rates of growth of the abuse of stimulants and of hallucinogens is less than the rate of growth of opioids.

Is that a fair assessment?

DR. CONWAY: That is fair to say. And, in fact, in some cases, the rate of growth for the other drugs you mentioned is zero. It's flat.

DR. KIRSCH: Dr. Bickel.

DR. BICKEL: I have two questions, one for Dr. Governale and one to Dr. Conway.

Regarding Dr. Governale, on graph 14, which shows the age participation graphs of individuals receiving prescription stratified by age and sex, there's a mode around age 50 to 59. I was wondering if you could indicate whether you thought that was a cohort effect, an age effect, or an age by cohort effect.

DR. GOVERNALE: I think the data, we're just looking at the number of patients receiving these prescriptions in the outpatient pharmacy setting. So they're looking at individual unique patients, and they're not being double counted in the years over the --

DR. BICKEL: So I guess what I'm asking, if we were to go 10 years back or project 10 years in the future, would that mode move forward or would it stay at age 50-59?

DR. GOVERNALE: We'll have to take a look at those other years, but I don't have the data on that right now.

DR. BICKEL: Okay. Thank you.

Dr. Conway, I was wondering if there were any set of data that you're aware of that reflects the percent of individuals who are exposed during adolescence who later become addicted to those substances.

DR. CONWAY: I am not aware of any recent data on that. I know Jim Anthony years ago in "Psychopharmacology" published a piece comparing rates

of dependence given use across different classes. It wasn't done, as I recall, among adolescents. It was done, I think, using the National Co-morbidity Survey, so for adults.

The question if applied to adolescence, exposure, I don't know of any data. We do believe, however, that adolescence is a period of considerable vulnerability for addiction. We know this, as you know, from animal science in that exposure to substances during adolescence may alter the brain in significant ways increasing the risk of addiction later. I could look for human data on that to directly answer your question and get back to you.

DR. KIRSCH: Dr. Morrato.

DR. MORRATO: Thank you. I have two questions, one for Dr. Governale and one for Dr. Dormitzer. I'll start with the question for Dr. Dormitzer.

Trying to better understand the patterns of use between immediate-release and extended-release long-acting, and I'm wondering on your slide 8 in which you're presenting some data from the National

Survey on Drug Use and Health and that slide talks about where pain relievers were obtained -- I'm wondering whether or not if there was any sub-analysis or stratified analysis where you could look at that, depending on whether or not they reported using immediate release or an extended release in terms of sources of obtaining the drug.

DR. DORMITZER: I didn't do the analysis, but my understanding was it was as a group, pain relievers as a group. So it does not split out between immediate release and extended release. SAMHSA did do an analysis for OxyContin but not for the other extended-release products.

DR. MORRATO: And did the OxyContin patterns resemble the total, do you know?

DR. DORMITZER: I don't know. I was wondering if Nick Reuter knew.

DR. MORRATO: Okay. Thank you.

My other question is to Dr. Governale. If I look at your slide 12 where you are looking at the percent of new TRXs dispensed, and I wanted to make sure I understand how you were defining "new."

If I understood it correctly, it was any opioid in the previous month or only opioids within that subgroup? So, for instance, is a new patient on an immediate release new to immediate release in the last month or new to all opioids, and they're just showing up in the immediate-release group?

Does that make sense?

DR. GOVERNALE: Those were all opioids, any immediate-release or extended-release opioids. They had not had a prior prescription for any opioids.

DR. MORRATO: And then did you do any sensitivity analysis going beyond just the past month, let's say the past year, of trying to understand, sort of switching patterns?

DR. GOVERNALE: No, we didn't, no.

DR. MORRATO: Any switching analyses between the categories?

DR. GOVERNALE: The switching data were also presented. I didn't really go into that while I was presenting. But there were a slightly larger proportion of switching for the extended-release opioid products, but it also could have included

patients who were also adding on as well as switching among the opioids.

DR. MORRATO: Yes, and so again, it's across classes. It's not --

DR. GOVERNALE: Right.

DR. MORRATO: Okay. Thank you.

DR. GOVERNALE: And sorry. To get back to your previous question about the patients in ages, we're limited by our databases because we can only go back to year 2002 for age and sex data. So that's a good question, but we couldn't go back beyond that year.

DR. KIRSCH: We have a very fully agenda today, so I'm going to cut the questions off at this point. We'll have ample time tomorrow to ask lots of questions and have lots of discussion.

The next talk will be given -- Dr. Hertz is unable to be here today, so Dr. Rappaport will provide us with the next talk.

DR. RAPPAPORT: Good morning. So far today, you've heard about the scope of the problem, and next we're going to be moving into discussing the efforts

made by the FDA and other government agencies to address the problem. Following that, we'll be presenting information regarding REMS in general and also how our specific proposal for the opioid REMS developed.

This afternoon, you'll also be hearing about the challenges for finding the right metrics to evaluate an opioid REMS as well as some additional efforts that FDA plans to develop under our Safe Use Initiative and information on the potential use of continuing education to incentivize prescriber education. And finally today, you'll hear from the industry regarding their own experience and efforts to develop an opioid REMS.

So first, I'm going to be talking about labeling changes and risk management programs for the extended-release opioids that we've implemented over the past 10 years in response to this growing problem. We've had public discussions of risk management plans and labeling for these products at prior advisory committees, and I'll also briefly touch on those meetings as well.

In 2000, the agency first received reports of problems with prescription opioid abuse, especially involving OxyContin. The problems included crushing of the tablets to defeat the extended-release properties, misuse by several different routes, and the unfortunate outcomes of addiction, overdose and death. The reports of abuse were not evenly distributed in the U.S. Several states, including Kentucky, Virginia, West Virginia, Pennsylvania, Maine and Ohio, had substantially higher rates of abuse and misuse of OxyContin compared to other parts of the country. It was also striking that the reports of abuse did not just involve addicts experienced with using illicit drugs but also included patients being treated for pain as well as recreational drug users, primarily young adults and teenagers.

We were concerned about the abuse liability of oxycodone, the impact of both the extended-release formulation and the large amount of oxycodone available in a single tablet, the ability of abusers to defeat the extended-release characteristics of the formulation, and the aggressive marketing and

promotion of the product.

The labeling was reviewed to assess whether there was any misleading information and whether additional information could be added to address the concerns. Labeling changes were made to warn that the extended-release opioids were not to be used when immediate-release opioids were adequate and to enhance the existing warnings so the prescribers would understand the potential risks associated with the product.

Review of the OxyContin label promoted a review of the other extended-release opioids, and changes were made to several sections of the package insert of these products starting with the indication. The most common indication for the extended-release opioids at that time was for the management of moderate to severe pain where the use of an opioid analgesic is appropriate for more than a few days. This was amended at that time for the management of moderate to severe pain when a continuous around-the-clock analgesic is needed for an extended period of time.

In addition, to emphasize the proper use of the extended-release opioids, we also added that these products are not intended for intermittent dosing or for use on an as-needed basis and that they are not indicated for the treatment of pain in the immediate post-operative period if the pain is mild and/or not expected to persist.

A boxed warning was added to these products to call attention to the potential for overdose, abuse and misuse and to highlight the proper treatment population. The boxed warning included language that more consistently describes the potential for abuse of a Schedule II opioid across the class, and it included explicit warnings that the potential for abuse should be considered when prescribing extended-release opioids.

The boxed warning also included language from the updated indication describing important features of proper patient selection, and it included a description of risk factors for opioid abuse that could be used by the prescriber to screen patients.

The safe use conditions regarding the

importance of not cutting, breaking, chewing, crushing or dissolving the extended-release products to avoid the risk of dose dumping were also standardized in the extended-release opioid labels. In addition, updates were made to the drug abuse and dependence section of those labels.

Now I'm going to discuss the history of the risk management plans for the long-acting extended-release opioid drug products. The first risk management plan for an oral extended-release opioid was developed in 2001 for OxyContin. The risks identified for mitigation were abuse and diversion, improper patient selection and accidental pediatric exposure.

This plan was modeled after the risk management plan designed for Actiq, which is an immediate-release oral transmucosal fentanyl product that had been approved a couple of years earlier.

The risk management plan focused on education, surveillance and intervention when a signal of misuse or abuse became apparent. The educational component targeted healthcare providers using a

variety of materials. The surveillance elements included existing databases as well as the development of the RADAR system, now a freestanding system, that uses drug treatment programs, contacts with law enforcement and contacts with those who follow abuse and addiction trends related to treatment and to research.

As the agency worked to address the problems of prescription opioid abuse and misuse, several public meetings were held that focused on the extended-release opioids. The first was a meeting of the Anesthetic and Life Support Drugs Advisory Committee, also referred to ALSDAC, held in January of 2002. And while they recognized the growing public health problem of abuse, the committee members expressed concern that any risk management plan that would restrict opioid treatment could prevent the appropriate use of these products and reduce access to these important analgesics by patients who needed them.

In 2003, a second meeting of the ALSDAC discussed risk management plans with particular

attention given to modified-release products. The key components of risk mitigation identified by the committee members at that time were prescriber education, surveillance, assessment of the source of diverted drugs, and assessment of the impact of risk management plans on opioid prescribing practices.

Then more recently in 2008, at a third meeting of the ALSDAC held to discuss a new formulation of OxyContin that had been designed to thwart tampering with the extended-release formulation, the members expressed a preference that any risk management plan be directed at the entire opioid class, not just the extended-release products.

So now you've heard about the problem of prescription opioid abuse and misuse that affects both patients and non patients. And I have described some of the FDA's efforts to intervene in this problem. You'll now hear from some of the additional agency efforts to reduce the abuse and misuse of these products followed by some of the work in this area undertaken by other federal agencies. And later, you'll hear about development of our current extended-

release and long-acting opioid REMS proposal. Thank you.

DR. KIRSCH: Thank you.

The next speaker is Ellen Frank.

MS. FRANK: Good morning. My name is Ellen Frank. I'm the director of the Division of Public Affairs in the Center for Drug Evaluation and Research.

The division of public affairs falls under the office of communications, and we began this division about 15 years ago, and that's when I first came to FDA. And at that time, it was recognized that CDER could play a major role in educating the public, both consumers and health professionals, about how to use medicine safely. So over the years, our division really began to form three functions. We did internal and external publications. We focused on helping out with media relations, specifically focusing on the trade media. And we began some interesting education programs. And the purpose of our education programs was to let health professionals and consumers know that there's important messages that FDA has to tell

the public. And we felt as an agency we had a goal and a mission to do this.

So we've developed several education campaigns over the last 10 to 15 years, and what I'd like to share with you today is some of those campaigns that are specific to the abuse and misuse of prescription pain relievers. Several of these campaigns we've done independently. Most of them, we've done in partnership with other organizations. I'll give you a little bit of background on some of them and tell you what we've done and what we're continuing to do.

This is a list of the education campaigns that we've been working on specific to the misuse of prescription pain relievers. We have one on methadone that we did in conjunction with SAMHSA. We did one on the misuse of prescription pain relievers, targeting older adults; the misuse of pain relievers, targeting teenagers; prescription drug abuse, information geared towards the parents of teens, and we did that with the Partnership for Drug-Free America and also worked together with the Office of National Drug Control

Policy.

We recently began a program called Medicines in My Home, and I'll talk a little more about that. And then we're currently working with the NCPIE and SAMHSA on doing a tool kit for college students, helping them figure out what dangers they might be coming into if they use these prescription drugs inappropriately. And the college students are using these medications thinking that they're safe because they're approved, and they're using them not for medical use but for recreational use, and there's a lot of harm being done to them and even death.

I want to just give an overview when we do our education campaigns of the kinds of materials that we develop and some of the ways that we'll disseminate. We do have a limited capacity at FDA to get information out, but through our partners, we're able to expand that reach. Most of the time, we focus on products like brochures, fact sheets, posters. Everything we produce is on our website. It's open to the public domain, and anybody can tap into it, reproduce it, use it. Sometimes we even work with

organizations to put their logo and FDA's logo on these products. We also allow any organization to link to our website.

We especially think there's a really good benefit to getting this information out at the point of purchase, at the pharmacies and supermarkets where patients and consumers are going to purchase these medications, that when they receive their prescription at the pharmacy counter, they also get this information in their hands.

We have a patient safety news team that produces videos, and we're currently using the latest social media technology such as YouTube and Facebook, tweetering, blogging to get these out to the intended audiences.

We have always developed public service announcements because you never know when we're going to get remnant space in a magazine or a newspaper or on TV. We don't have the dollars to put these ads often into the magazines and TV because it's so expensive, but quite often, we are given free space to do that.

We develop radio ads as well; there is an excellent way because we believe that people receive their information through a variety of channels. Some people are more apt to read something where others will maybe listen to it via audio or TV or radio.

Then we proactively put information into newspapers and magazines trying to get this information out again in another vehicle. And most of our dissemination is done not only through our website but through the websites of our partners as well. And again, I'll be mentioning partners often because they're key in helping us get this information out.

I'll begin by talking a little bit about the education campaign we did in conjunction with SAMHSA on methadone. SAMHSA and FDA came together because we both had a message about this subject. SAMHSA recognized that methadone, being used to help people with addictions, could be misused and abused. And we at FDA recognized that folks who were using this as a pain medication also had potential for misuse and abuse. And what we found is that also prescribers needed to be educated. They were giving too much too

soon.

The information that we wanted to get out to patients in terms of this as a pain reducer is that a lot of them weren't aware that when their pain came back, they thought the medication was out of their system. And if they knew through education that that medication was still in their system, they might not have been apt to take additional medication and cause an overdose. So information like that is key and important, and we felt an obligation to get that out.

We developed these public service ads, again, in conjunction with SAMHSA, and the goal here was to target the older population, those who were taking maybe five or six or seven medications at a time who really didn't intend to overdose or misuse but weren't reading the label, weren't taking the correct dose or talking to their doctor. So these messages were to get their attention.

This was an education campaign again with SAMHSA. We've done a lot of work with SAMHSA. We both realize we have a lot of the similar messages and missions that we want to get out to the public. This

was geared towards teens, and we really kind of took the shock effect on this. And we wrote a brochure, and we did these public service ads to get the attention of 18- to 24-year-olds who might be going to a party and sticking their hand in a bowl and grabbing a medication thinking that these are all prescription medications, can't do them any harm because they're approved, not realizing that these medications could kill them even if they took them just once. If they were taking OxyContin and it was extended-release, they might not release that that could be very harmful if they crushed it or took it in a way that it wasn't intended.

So our goal here was to get this information out to that population, and we did this through college campuses, bus stops at college campuses, and also, in high schools through high school counselors. And there's really no end to the ways that we can reach teens, and we're always looking for new avenues to get these messages out.

About a year ago, we partnered with the Partnership for Drug-Free America and did this ad that

appeared in Newsweek. And this ad was geared at parents of teenagers, and the goal was to educate parents to look for the signs that their teenagers might be depressed or might be falling to peer pressure, and that they might be using medicines that they might find in their homes and get from friends and family; and that if parents could recognize the signs and also recognize the signs of abuse, that they can step in and make a difference. It was also important that parents take a role in storing and disposing their prescription medications properly so their teens couldn't get a hand on it.

We and many others, as you can see at the bottom of this open letter that appeared in major newspaper, had a partnership with the Office of National Drug Control Policy. And again, this was a message for parents. It was telling parents how easy it is for teens to access these medications in the home and that, also, teens don't see these medications as being harmful. And it was giving parents resources on where they can go to get help and how to recognize if their teens needed help. It was basically

educating parents to protect their children.

We recently developed Medicines in My Home, which is an interactive web program accompanies by hard copy materials such as brochures and posters. And the goal of this was to reach middle school children and to get them at that age so that they can learn early on how to use medicine safely. This program is done in a way that gets their attention. It's interesting. It's interactive, so it keeps their attention. And we're trying to get many schools to incorporate this in their curriculum.

This program focused a lot on OTCs, but there also was an element in here about the safe use of prescription medicines. And its goal is to teach younger children that they should read the label, follow the correct dose, make sure they're not taking too much of the same active ingredient, talk to a parent if they're going to take a medication, and definitely make sure that they have a prescription and that they're taking their medication as the doctor prescribes.

There's a wealth of information in this

program that's written in a language that the younger generation can understand, and it's a really wonderful resource. And I encourage anybody who's interested in looking to see how they can use this to further disseminate, it would be greatly appreciated.

As we move to the future, we know in the past that we have done some things to help folks use these medicines safer. Our education campaigns are just one way of getting the message out, but we don't really know how effective we are. We haven't really had the capacity to do the baseline research, and we haven't had the capacity to evaluate how effective these programs are. We know it can't hurt, but we just don't know really how helpful they are.

The goal is for us to expand what we're doing, and in the future as we build these elements into the opioid REMS education, that we want to do more research and evaluation as to how effective our education programs are. We appreciate any thoughts that any of you have on how we might be more effective in moving forward, and we're always seeking partners to work with us in figuring out what messages we

should be developing, what ways we should be getting it out. And we know that education works. We know that it's going to help support and reinforce the opioid REMS program, and we're looking forward to working with all of you in the future to do that. Thank you.

DR. KIRSCH: Thank you.

We will now take a 10-minute break. We will reconvene again in this ballroom in 10 minutes from now, which on my watch is 10:25. Panel members, please remember that there should be no discussion of the issues at hand during the break amongst yourselves or other members of the audience. Thank you.

(Whereupon, a recess was taken.)

DR. KIRSCH: The next speaker is Dr. Nicholas Reuter.

Is Dr. Reuter here?

MR. REUTER: Right here.

DR. KIRSCH: Great. Dr. Reuter, would you begin your presentation?

MR. REUTER: Thank you, and thanks to the committee. I'm Nick Reuter, not Dr. Nick Reuter, but

Nick Reuter with the Center for Substance Abuse Treatment that's part of the Substance Abuse and Mental Health Services Administration. I want to thank the chairman and the committee for allowing SAMHSA and CSAT to participate in this important conference.

I think I'm here to talk about what we've tried to do at SAMHSA with risk management on two specific opioids, those being the opioid treatment medications methadone and buprenorphine. And we've done quite a bit with this starting -- at least for a decade now.

Just a little bit of what I'll talk about in the next 10 or 15 minutes is a little bit on the survey trends, not much because you've heard a lot of that already this morning. What we've done on practitioner prescriber education and training, focusing on this modality called office-based buprenorphine, which I'll characterize as a risk management plan that Congress put into a specific law, the Drug Addiction Treatment Act; talk about what we're trying to -- manage risks in methadone

maintenance treatment programs through CME training and then how that expanded into opioids prescriber CME education and training for opioids use for pain treatment.

Some of our other prevention-related activities at SAMHSA would include NASPER grant, prescription electronic monitoring programs and what we're trying to do with that federal grant program, very little on consumer education because Ellen Frank presented most of that already.

I think what you're learning this morning is that prescription drug abuse is a problem. Prescription opioid drugs are very valuable medical products, but they are across several national surveys showing to be a drug abuse problem. That includes our National Survey on Drug Use and Health, the Drug Abuse Warning Network, the DAWN emergency department medical examiner, Monitoring the Future, and one that wasn't presented yet, the Youth Behavioral Risk Survey with the Center for Disease Control.

This particular measurement was not presented this morning. This is past month use of

select illicit drugs. And past month use is what we at SAMHSA interpret to mean currently using illicit substances. It's held steady for the last six years at around 8 percent. Eight percent of the U.S. population over age 12, that translates into around 21, 20 million people.

Third from the top is what we call current nonmedical use of prescription drugs, and there's some good news there in that between 2006 and 2008 and again in 2007 and 2008, significant decreases in current misuse of prescription drugs. That's 2.5 percent of the population. It translates into around 7 million people currently misuse prescription drugs.

What's driving that, the highest contributor to that is clearly narcotic pain relievers. And this has held steady for the last six years at around 2 percent, translating to around 5 or 6 million people currently nonmedical users of prescription pain relievers.

In response to one of the questions I heard earlier this morning, how some of the other prescription medications are trending over the years,

you see tranquilizers, stimulants and sedatives holding steady and in the case of stimulants, they've actually decreased in the number of current nonmedical users over the years.

So focusing on prescriber education and training, the Drug Addiction Treatment Act of 2000, I'll also talk about our opioid treatment program, continuing medical education program. That's targeted towards methadone used in addiction treatment. And then on our opioid prescriber, continuing medical education.

DATA 2000 is a federal law that permits certain physicians, not all, to prescribe certain narcotic medications for opioid dependence. So Congress put some provisions in there to restrict this as part of risk management. To be eligible, a physician must have a medical license, a DEA registration and must be qualified. The qualification could be credentialing or the qualification could be -- and this was set right in the federal law training, eight-hour training. And the law actually said the training could be electronic training, and we

interpret that to mean computer-assisted or online training.

The DATA 2000 put restrictions, only certain medications. It had to be a Schedule III medication. It had to be approved specifically by FDA for the indication of opioid dependence or opioid addiction. I guess the biggest limit overall is physicians could only treat a limited number of patients, no more than 30, and it later changed to allow physicians to treat up to 100 patients after they've had a year's worth of experience.

So we sat down and decided that we had to develop a training curriculum. We worked with specialists and experts in addiction treatment and developed a treatment guideline. We supported training. We had to jumpstart it. We went out and trained the trainers who would be the vanguard of providing this eight hours of continuing training or education so physicians would be eligible to prescribe the approved medications for addiction treatment.

This is a very rough estimate, and this is an estimate to train physicians in a live venue for

eight hours of CME, around $20,000 to train 100 physicians or educate 100 physicians in an eight-hour live CME training session. That includes a lunch and faculty costs and everything that would go along with that training.

Just an update. As of a few weeks ago, we've certified under this program, that's verified all their credentials and qualifications, 19,000 plus. We've trained almost 26,000 physicians under this. And the ratio is that around two-thirds of the physicians trained, or educated under this program, completed it in live treatment settings, and one-third of them completed their training via the Internet or other kind of electronic online features.

Now, just a brief discussion of does this training change practices. We convened a buprenorphine summit a few weeks ago, and this was one of the questions that we asked. Some work has been done with this. This is a particular evaluation conducted by the University of Kentucky with permission of Dr. Lofwall, best practices in buprenorphine prescribing, improving treatment in

Appalachia and Wisconsin through CME.

They did an evaluation component to some very structured continuing medical education that they provided on buprenorphine in addiction treatment. They actually did four surveys, one conducted prior to beginning the CME, onsite immediately after the continuing medical education was completed. A month after, they followed up one month after to assess the physicians, and three months after, the CME was completed and a Amazon gift card was included as an inducement to complete those post-surveys.

This is what we wanted to see. This is an important finding. I don't know how well you can see that, but on the left axis, it's the percentage of doctors, and on the X axis, it's the one who knew the average daily maintenance dose of buprenorphine for addiction treatment. And you see at the baseline, it was around 25 percent, and one month afterwards, it had increased to 60 percent, and then after three months, it held steady at around 58 percent. The statistics were significant after the three-month interval compared to baseline.

Then if you look to the next set of columns to the right, you see that the higher dosages, the physician perception, did change after the CME was completed, immediately afterwards, one month and three months afterwards. So it shows that the physician attended the CME training and did change at least their understanding of what the average daily maintenance dose of buprenorphine should be.

There were several evaluation criteria included in this study, and they also looked at knowledge of the buprenorphine half-life. At baseline, physicians reported that around 45 percent of them were aware that it was 37 hours. And then immediately after training, that jumped up to almost 100 percent, and it held steady. At three months out, it's statistically significant compared to baseline at around 85 percent.

We've also conducted opioid treatment program continuing medical education. This is for the -- what we hope to do is get to the 1200 opioid treatment programs in the U.S. and educate them on methadone.

Just to follow-up to one of the shortcomings in the denominator data for the DAWN analysis, I thought it'd be confounded by the number of patients or the amount of methadone that's dispensed by opioid treatment programs. That really pales in comparison to how much methadone is prescribed and dispensed through pharmacies for analgesic purposes.

My rough estimate is that there's around 260,000 people who receive methadone through the 1200 opioid treatment programs in the U.S, and there's around 750 to 760,000 individuals who receive methadone prescriptions in a given year dispensed by pharmacies for analgesia. So the opioid treatment contribution to this is much, much lower.

So what we do is we go into a state or a region, we focus on risk management. It's our effort to reduce the risks associated with methadone treatment for addiction. We include a pre- and post-test, a nine-question questionnaire. We've completed it in nine states, and we estimate it costs around $30,000 to educate around 100 health professionals through this eight hours of CME or CEU.

Probably more important to this audience is the physician education on opioid prescribing that we've been pursuing for the last two years. Someone earlier put up the slide of Scott Fishman's book on appropriate opioid prescribing. What we do with this CME training is to teach Dr. Fishman's book.

These are the things we focus on, the problems we see with patients who are prescribed opioids for a persistent pain; deciding whether or not to prescribe an opioid, the pharmacology; emphasis on methadone because methadone's contribution to overdose, and overdose mortality seems to be more acute; steps to take if you decide to use opioids in the treatment of persistent pain; what you should do if you decide not to use opioids in the treatment of persistent pain; and a lot of emphasis on this practical side of patient monitoring, which I think is important to today's endeavor; how do you use the state prescription drug monitoring program; how to screen patients, not just drug urine screening or drug testing but using formal screens; what to do if a patient reports a lost prescription, very, very

practical things; and then a session on when and why and how to stop prescribing opioids and manage the patient with another treatment approach when it appears there may be abuse or diversion associated with that particular patient's opioid use.

In the last two years, we've gone out and planned this training with state medical societies. It's important to include those. The medical boards in the state are interested in these. Demand is great. We've been out to 19 states, and many, many states approach us hoping that we'll bring this opioid prescribing training to their state.

Just a rough estimate, there's probably been around 11,000 physicians that have accessed this either through live training or online training. We've taken the four- to eight-hour CME training and condensed it down to a 90-minute webinar, which is available for free through the National Association of Community Health Centers. MedScape, the world's largest medical education website, has also developed a web-based version of this, and I've included the links here if the committee or others would like to

check and go through that.

Just reading through some of the comments that were submitted to the docket, there were questions raised about can providers and prescribers be reimbursed for screening patients, either drug testing screening or screening and brief intervention; identifying patients in their population who have substance abuse issues. And is it worth the physician's time, I guess was the question, to do that. Particularly, the comment in the docket was the patients have to pay for this screening. It's usually not covered. The screening and the evaluation is not covered under private and public health insurance. And we're trying to move in a direction where these kind of screenings and additional evaluations from physicians can be covered, have developed these codes for Medicaid reimbursement, for alcohol and drug screening. They also get a reimbursement code. Modest amounts, as you see here, $24, and $48 and commercial CPT codes was the specific question in the docket. So there can be reimbursement for screening and brief intervention for the substances in

physicians' offices.

We didn't leave it at just CME training as part of our risk reduction endeavors at SAMHSA. We have a physician clinical support system, one for buprenorphine and addiction treatment, and the newer one is for methadone. And this is methadone for addiction and methadone for pain treatment.

So if there is a practitioner or prescriber out there who has a complicated case for methadone in pain treatment, they can connect with an experienced pain treatment specialist or they can connect with an experienced addictionologist and go over those cases and obtain resources to help them effectively and safely treat the patients. These are supported by SAMHSA grants.

A little bit about our involvement with the National All Schedule Prescription Electronic Reporting Act, a lot of discussion of that in the docket for the opioid REMS. In response to Dr. Kosten's question, from what I understand, the VA hospital physicians do access the prescription drug monitoring systems that are in the states where the VA

hospital is located, but a bigger problem is that the VA system does not report in to the state prescription drug monitoring program, something we hope to have fixed soon.

So there is a resource for VA physicians who are treating patients with pain and opioid analgesics to find out what other prescriptions that patient may be filling in the state.

Our goal and the goal of NASPER is to get prescription drug monitoring information in a timely manner to physicians so they have that information available in front of them when the patient is before them to be evaluated for what to prescribe and how much.

There's been some real expansion of prescription drug monitoring programs. They've been in place for around 50 years now, give or take. Only recently, with the addition of Florida, can we say that 95 percent of the U.S. population is now covered by a state prescription drug monitoring program. That would exclude the state of Maryland. There is no prescription drug monitoring program in this state.

What we try to do at SAMHSA with this system in awarding grants to states is make it a condition that for a state to get a grant under NASPER to expand or improve their prescription drug monitoring program, they show us that they're getting information to physicians. Instead of relying on the physician going through the process of obtaining an account for a prescription drug monitoring program and accessing the account, we're going to require that states use the information that's in their system and send reports to physicians so that they know that there may be a patient in their practice who is exhibiting drug-seeking behavior who may be doctor shopping. So that's what we're trying to do this year with our involvement with NASPER.

You heard some talk about the efforts with FDA on consumer education. We divide it up into three sections, and it really is with the National Council on Patient Information and Education. The campaign is called "Not Worth the Risks Even If It's Legal." And it's divided into three phases, talking to parents and teenagers about medicine abuse; the second phase,

talking to teen influencers about medicine abuse; and the final one that Ellen talked about, talking prescription medicine abuse that's targeting college-age students.

So to summarize, I think from SAMHSA's perspective and what we're trying to do in our specific risk management efforts with methadone, buprenorphine and all prescription opioids is that prescription opioids abuse and misuse is a significant public health problem.

I think the buprenorphine opioid education training available is widely available. It's workable. It's a certification program that we think can be implemented. I did a rough estimate of the cost, of what it costs SAMHSA to certify those 19,000 physicians, and it breaks down to around $50 per doctor to verify their credentials. It doesn't say how much it cost to establish a CME program and to get doctors to complete CMA training, but to verify that they've met those qualifications, around $50 per doctor.

We think that monitoring systems like NASPER

and prescription drug monitoring programs should provide useful information to prescribers. But we think it's a comprehensive effort that's going to be needed on this, including what's going on here today. Prescribers, dispensers and consumers all have to be brought together to reduce this problem. Thank you.

DR. KIRSCH: Thank you.

Our next speaker is from the DEA, Richard Boyd.

MR. BOYD: Good morning. I'm Rick Boyd with Drug Enforcement. I was asked to do a presentation on how DEA registers anybody that handles controlled substances. I'm going to cover a quick historical perspective, the mission of diversion control, registration as a cornerstone of the Controlled Substance Act, who must register, and a snapshot of the population currently, the DEA number construction, our website, and then basically, some info on our registration database.

Prior to 1914, there was really no comprehensive federal legislation. In 1914 with the passage of the Harrison Drug Act, was the first

enforcement and control the federal government showed for narcotics. Over the years, various legislative actions occurred, and as you can see, the responsibility for that merged and changed to a variety of different agencies.

In 1970, the Controlled Substance Act was passed, and that basically replaced over 50 different pieces of legislation that controlled drugs. It established a single source for both narcotics and psychotropic drugs, and it established five schedules that classified the controlled substances based on their medical properties and the potential for abuse.

The CSA established a closed system. Basically, it allows for DEA to be able to track and account for any controlled substance from importation through manufacture through wholesale down to the ultimate end user. It also facilitated the creation of the compliance program which today is what we call the Office of Diversion Control, and that's where my office resides.

Probably everybody is aware of the diversion control's effort as far as preventing and the

detection and investigation of any diversion. But the primary purpose of diversion control is to ensure an adequate supply and an uninterrupted supply for legitimate medical needs.

The CSA's controlled system is basically five components. I talked of the scheduling based on the potential for abuse, registration of anybody that handles controlled substance, recordkeeping, security, and manufacturing quotas.

Any person or entity that handles controlled substance must register with DEA. They have to apply using one of four forms, and that's based on the type of business that they're conducting. They have to have a state license. The CSA requires that the state authority be present prior to DEA issuing a DEA registration, and they also have to be in good standing from the medical community as well as comply with DEA security requirements.

With the passage of the CSA in 1970, there was approximately 2,000 practitioners that had been registered and entities that had been registered. Over the years, that has grown to 1.34 million people.

Taking a quick look at it, if you look at the chart on the various types of business, 93 percent of that 1.3 million are, in fact, individuals, practitioners, physicians, MDs, DDSs, DMDs, as well as nurse practitioners and physician assistants.

The wholesale side, what we call the wholesale side of the operation, that 13,000 of those are more the brick and mortar, and that stays fairly constant. The retail side of it, the practitioners and the midlevel practitioners, grows at about a 3 percent per annum.

Everybody I think, is aware of the DEA number. It is, in fact, a unique mathematical formula, and it's very easy for pharmacists to be able to check just by looking at the number and knowing the formula. The last digit is the check digit based upon the addition and multiplication of the previous six numbers. I don't expect anybody to actually realize what the formula is. Just understand that there is, in fact, a formula and just by looking at a number, you can tell whether it's, in fact, a valid number or not. And I'm going to get into a validation tool that

we have on our website toward the end.

One of the issues when I came to DEA seven years ago was to modernize. You can imagine with 1.3 million registrants and everybody sitting there submitting paper, we basically process 400,000-plus applications and renewals a year. We moved to the website in 2004, and basically, everything that we do now, 95 percent of our processing is done on the website via the practitioners or the MLPs. It's all encrypted.

For security reasons, we do not connect the database that retains the registrant's information. That is not connected to the website. All the information on the website that's passed via encrypted transactions, we download in a micro-burst in the middle of the night, and so therefore, you don't get any potential for hacking into the CSA database.

Picture of our website. From this website, basically, the practitioners can apply. They can renew. They can make changes. They can add schedules, subtract schedules. And we'll get into some of the other tools that are available there.

It's very simple for the application, assuming they read what they require before they click the "begin process" button. But what they do basically is once they apply, once they get into it, it takes about six minutes on average for a practitioner to do a new application. There's five sections. It's as fast basically as he can type his information in. It's general information of his name and his address, what schedules they want, the state licensing information, some background, security background information and then the payment information.

Changes, we get about 10,000 changes per month where doctors and mid-levels are trying to make changes, either a name or they're changing their address. All that's done interactively via the web. You can also order the duplicate certificates as well as the 222 order forms for ordering controlled substances, Schedules I and II.

The log-in for security requirements requires exact matches of six different elements that only the practitioner should know. Four of the six

elements are found on the certificate itself. The other two, the Social Security number and their tax ID, that should be from a privacy standpoint, only the practitioner should know that himself.

Any application, any renewal, any change that is input into the website, we've designed and built an automated work flow that based on the type of business activity, the requested change, where that person is located, the program automatically electronically sends it to the local DEA field office for review and approval. And that's basically almost instantaneously. We do do it at the nightly download. But if you apply today, by tomorrow morning, that new application is at the local field office for review.

Registration and validation, I mentioned earlier. Any DEA registrant can validate another registrant. In order to log in to do that, basically, it's three pieces of information, the Social, the last name and the DEA number. They then get a box that they type in if they want to verify another DEA number. And what they get back is what the information found on the 223, what DEA considers to be

public information. And that is available for any DEA registrant to be able to do.

Any questions? Because that was it, a really straightforward process.

DR. KIRSCH: Thank you.

The next speaker is Dr. McLellan.

DR. MCLELLAN: Thank you very much. I want to give a little overview of work ONDCP, Office of National Drug Control, is doing on this issue, and the title pretty much sums it up. We think it's a very -- and pain management itself is an important part of the problems that have been amply described here in terms of diversion and overdose. And there is, we think, time to call on physicians to take a look at their responsibility, but not just physicians. We think it's time for patients to take more responsibility and the government as well. And so I thought I'd talk a little bit about the problem, use two studies that illustrate some of the complexity to talk a little bit about our rationale for our approach and then talk about that approach.

Since 1997, and this has been discussed

earlier, pain management societies got together and agreed upon two things, basically that pain had been under-treated and that there was less compassionate care than was reasonably available and could reasonably be done. And with that came the consensus decision to expand the use of opiates. And 10 years later, now we have opioids as the most prescribed medication. By the way, obviously, the population is older. It's not the only factor, but we think it's a contributing factor.

Opioids are now the most prescribed medication. Pain management clinics are up 350 percent. As you've seen, methadone and oxycodone are up over that 10-year period substantially. I'm not saying it's necessarily a bad thing, just simply a fact. There is greater use of these medications.

But there have been other changes as well. And by 2008, physician arrests have been up 250 percent. We've all seen the opioid overdose reports. These are overdose deaths. Overdose incidents of other kinds are even higher. The opioids deaths are 90 percent and other incidents are 110

percent increase. And I find this startling, actually; opioid overdose death is now the number two cause of accidental death in the country. In 10 states, it's the number one cause of accidental death. It eclipses automobile accidents and gunshots wounds. It's remarkable.

Here's a related example from the NHTSA report of 2007 where they did a random voluntary roadside stop, and with a buccal swab looked at substance use. And it's the first time that that was done. It was a voluntary stoppage. Most of it was at night and on weekend nights. And they had about 6,000 drivers tested. Illegal drugs were about 11 percent, but opioid medications and benzodiazepines were 5 percent. And the quality of the testing was that it was able to detect specimens in the last three hours. So that's what this means, that these people were driving with these medications on board within the last three hours.

Now, you might say, okay, so there's a lot of opioids being prescribed and there are a lot of opioids incidents and overdose deaths. But what does

that mean? Whose fault is it? What should be done? And here are two studies that I think illustrate two sides of the problem. Both of these have been published.

The first one I'll talk about is the Hall, et al, study in JAMA, and this was a West Virginia study. And we all know that West Virginia, like all the Appalachian states, has been particularly heavily hit by particularly OxyContin overdose deaths. Well, they studied 332 of the deaths in 2006 and looked at the case histories and prescription records. The death rate was alarming high, 18 per 100,000.

One of the interesting things to us was predictors. Predictors of opioid overdose death, there are the demographic ones that you can't do anything about, being male, 35 to 54 and low socioeconomic strata. But the ones I have highlighted here is the presence of a mental health or a substance use diagnosis, a history of a prior overdose incident, history in the record of a benzodiazepine prescription and/or being within 10 days of the scrip, particularly on a renewal, were all major predictors of an opioid

overdose death.

Now, here's the important point. Only 36 percent of the, quote, "prescribed" -- this is often called opioid prescription overdose. Well, only 36 percent of those who died actually had received a prescription, so 64 percent had not. Most had either gotten the drugs from some other source, and there's an additional proportion of patients who were found to have received -- they actually had received a prescription, but they had received prescriptions for five or more doctors, commonly called doctor shopping.

So in this West Virginia study, you might reasonably say, yes, doctors bear some responsibility here, but really, the great majority of the people who later died had been either dissembling or frankly, misrepresenting to the doctor. And since most of these cases were low back pain and pain where it was difficult to verify, it's hard to pin too much on the doctor. So that's Study 1.

Study 2 occurred on the other side of the United States in Oregon, and this is a study by Group Health. And it was a study of their overdose

incidents, and they looked at 3,000 incidents in 2008 and once again examined case histories and prescription records. I find it interesting because the death rate was still alarmingly high, not quite as high as in West Virginia, 11 versus 18.

The predictive factors were almost identical, again, a history of a substance use diagnosis or a mental health diagnosis, and the other factors that you now no longer see and neither do I. But they were the same.

The reason this is interesting -- and I put the studies side by side -- is here's a situation in a managed care environment, middle class, employed people, all had primary care docs and virtually no doctor shopping. And, once again, they were able to tell -- 27 percent. And these overdose deaths were not due to the doctor shopping or at least to the same extent, the disassembly (ph) that had characterized the first study.

But particularly disturbing was the fact that so many of these incidents might, at least with 20/20 hindsight, have been averted. Twenty-seven

percent of those who later died had had an earlier overdose incident, and it was recorded but nothing had happened. The diagnostic material, the presence of other medications that would interact, like benzodiazepines, was available in their electronic health record and had not been used.

So I think the two studies point out some of, not all, but some of the interesting parts of this problem. And you will see in our policies, we do not believe that any single group of individuals bears full responsibility or can by themselves take this very complicated problem on. But there's a piece of responsibility here for everybody.

Physicians are responding. You've heard earlier today. There are new society guidelines. We think this is appropriate. This is the position of ONDCP. We don't think government should tell physicians how to treat pain. We do ask physicians to reexamine the pain management, especially when it involves use of opioids, because unlike so many other medical conditions, here's a condition where it's not just the individual patient's welfare that is at

stake. This is an issue of public health and public safety.

And societies have responded. There are new guidelines, and those are two examples.

But there are practice elements that frankly, aren't being done that are part of those guidelines. Screening and diagnosis of substance use, even asking patients about their substance use history is not being done, patient contracting or agreements. Our data suggests that especially in single practitioner settings, it's not being done; patient and family education.

I should mention that most of the pain physicians that I talk about talk about -- and another problem that's in some ways the bookend to overdose and overdose incidents, so many people prescribed medications for pain are afraid to take the medications because they're afraid they'll become addicted. So for that reason and because of all the potential for harmful incidents to occur, we think patient and family education on safe storage, on proper use, on not sharing it is particularly

important.

Then a very simple thing that is no stranger to the substance abuse treatment world is not being done in other areas. Urine screens, prior to the original prescription, during the course of it and at renewal. And as Nick Reuter was just talking about, we're very positive about prescription drug monitoring programs, but there are problems there.

There are two prescription drug monitoring programs now. One, you heard about, the NASPER, done through HHS, and the other is the Hal Rogers Program done through the Justice Department. They're both very good. They were created with different purposes in mind, Justice, to catch cases of fraud, abuse and doctor shopping and the NASPER, to prevent overdoses.

There are problems with both. First is not all states are doing it. Second is the information doesn't share across state lines. Take Maryland, for example. We're within an hour of four states. So I could doctor shop in all states, and all four states could not see me as doctor shopping within that state but I have been doing it across the states. And then

there's this.

At least with regard to the Hal Rogers Program, less than 10 percent of physicians are using these programs. So we think these are tools that they still need development, but these are tools that can help this project and to reduce this really awful problem that we're having. So with ONDCP, Justice and Health and Human Services are working to try to harmonize these prescription drug monitoring programs, get full funding for them, get physicians to use them, give meaningful reports from them.

The other thing that we're doing as part of the ONDCP national drug control strategy is we have made involvement of physicians and primary care a major part of substance use treatment. In particular, we with HRSA and Indian Health Service, we are integrating substance use services into primary care settings in federally-qualified health centers and in clinics within the Indian Health Service. We think with this and giving physicians more experience and training in lower level substance use problems, mild to moderate addictions, and giving more availability

for patients who have early or emerging substance use problems to get care for their substance use where they get care for the rest of their medical problems, we think that's part of the solution.

So in summary, what I always say, it's the three Fs. It's physicians, families and the pharmaceutical industry. Each have a role to play in this. Families need to take more responsibility for safe storage and proper use. Physicians, we think, need to take advantage of the tools that are already there. Government needs to help make those tools better but also to reevaluate their prescribing practices, to do what every other speaker has said, make sure we maintain the benefits of these important medications without increasing the side effects. And then there are the distribution practices of the medications themselves.

I'm happy to say that FDA, CDC, DEA, NIDA and ONDCP are working quite well together in trying to develop the kinds of practices and policies that will bring an end to this. Thank you very much.

DR. KIRSCH: Thank you.

We are running behind time, so we're going to not have a question and clarification session. And rather, we're going to go on to the next session, and the presenter is Jane Axelrad.

MS. AXELRAD: My name is Jane Axelrad, and I'm the associate director for policy in the Center for Drug Evaluation and Research.

I'm going to talk today about the legal framework under which we're proposing to require a REMS for long-acting and extended-release opioids. The FDAAA REMS provisions built upon FDA's previous experience in requiring restricted distribution and other risk management tools when necessary to ensure that the benefits of a drug outweighed its risks. FDAAA authorizes FDA to require a REMS both before a drug is approved and after approval if FDA determines that a REMS is necessary to ensure that the benefits of the drug outweigh its risks.

If a drug has been marketed initially without a REMS, to require a REMS post-approval, FDA has to have new safety information. The actual definition of new safety information in the statute is

quite complicated, but basically, it boils down to new safety information is information that's tied to a serious risk associated with the drug of which FDA has become aware since the drug was approved.

The FDAAA REMS provisions, unlike previous authority, are enforceable. FDA can take enforcement action against a sponsor who introduces a drug into interstate commerce if they are in violation of the REMS provisions. The drug can be found to be misbranded, and FDA can impose civil penalties on sponsors for violations of the act.

FDAAA requires FDA to consider several factors when determining if a REMS will be required for a drug. These factors are laid out in the statute, and they are the size of the population likely to use the drug, the seriousness of the disease, the expected benefit of the drug, the expected duration of treatment, the seriousness of known or potential adverse events, and whether the drug is a new molecular entity.

The law provides that FDA has discretion to require a certain element of a REMS. These include a

medication guide if the criteria and our regulations governing medication guides, that's Part 208, are met; and a patient package insert if we find that the insert could help mitigate a serious risk of the drug.

We can require a communication plan as part of the REMS if we determine that such a plan might support implementation of an element of the REMS. We can require elements to ensure safe use under certain circumstances and an implementation system if the REMS include certain elements to ensure safe use. The only required element of a REMS under the statute is a time table for assessment of the REMS.

Medication guides were previously considered only part of labeling, but they may be included under the statute as part of a REMS if we decide that a medication guide is necessary to inform patients about the risks or instructions for safe use of the drug.

We can require the sponsor to develop and implement a communication plan as part of a REMS if it would support implementation of an element of the REMS. In such cases, we can require sponsors to inform prescribers and others about the risks of the drug and

protocols to assure safe use. However, under the statute, if an abbreviated new drug application is approved for a drug that has a REMS that includes a communication plan, FDAAA states that FDA must implement the communication plan for both the generic and innovator products.

Elements to assure safe use are the most prescriptive elements that can be required in a REMS. FDAAA provides that FDA may require elements to assure safe use when FDA determines that the drug is associated with a serious adverse drug experience and can be approved only if or would be withdrawn unless such elements are required as part of such a strategy. And for a drug that is approved initially without elements to assure safe use, before we require such elements, we have to find that other elements such as a medication guide, a package insert and a communication plan would not be sufficient to mitigate the serious risk.

In addition, FDAAA requires that the elements to assure safe use be commensurate with the specific serious risks listed on the labeling of the

drug and not be unduly burdensome on patient access to the drug. FDAAA specifies that to minimize the burden on the healthcare delivery system, elements to assure safe use must, to the extent practicable, conform with elements for other drugs with similar serious risks and be designed for compatibility with established distribution, procurement and dispensing systems.

FDAAA describes six specific types of elements to assure safe use that can be included in a REMS. Our proposal includes elements only in the first category, but I'm going to describe the other categories very briefly so that you'll understand the range of tools that we have to choose from in designing elements to assure safe use.

Let's look at each one in turn. First, a REMS can require that healthcare providers who prescribe the drug be required to have particular training or experience or special certifications. We can specify the type of training or experience, and we generally approve the content of educational materials that are approved with and then appended to the REMS. The training or certification usually covers the risk

of the drug and any of the particulars associated with safe use, such as limitations on the duration of the drug's use or its use in particularly vulnerable patient populations. It may also require prescribers to counsel patients about the risks and use of the drug.

Many of the REMS that we've approved with elements to assure safe use, and there are relatively few of those, also include pharmacy certifications. To become certified, pharmacies or pharmacists may be required to familiarize themselves and staff with the risks of the drug and the conditions to assure safe use. A REMS can require pharmacists to verify that the prescriber or patient is enrolled in the REMS program, enroll the patients themselves, and/or counsel the patients before dispensing the prescription.

The third type of element to assure safe use may require that the drug be dispensed only in certain healthcare settings. This element is directed at making sure that the patient getting the drug is in a healthcare setting designed to promote its safe use.

The fourth type of element to assure safe use may require that the drug be dispensed with documentation of safe use conditions. When a program requires documentation of safe use conditions, it usually but not always includes this documentation as part of enrollment of patients in a program.

As a condition of enrollment, the program may require patients to attest to the fact that they have read and understand the medication guide, if one is included in the REMS, and the particular risks of the drug. They may be required to agree to take certain tests like pregnancy tests or agree to follow-up monitoring such as blood test to monitor liver function, and they may also be required to agree to certain longer-term follow-up to identify long-term effects.

The fifth type of element to assure safe use may require patient monitoring, which can include, for example, periodic blood tests or follow-up questionnaires.

The last category of element to assure safe use is patients can be required to enroll in a

registry. In some cases, enrollment in a REMS program can act as a registry. It provides information on patients prescribed the drug, and it allows follow-up on adverse events and trends.

It's important to note that the elements to assure safe use are not mutually exclusive. There can be considerable overlap. For example, educational materials are very important components of several of the elements. FDA is working as we are developing REMS to standardize the elements, but basically, individual REMS are usually shaped based on the characteristics of the drug and the risks that the REMS is designed to address, and to some extent on sponsor preferences.

FDAAA specifies that a REMS can include an implementation system if it relates to certain elements to assure safe use. So if a REMS require certification of pharmacies, practitioners or healthcare settings that dispense the drug, if it requires that the drug be dispensed only in certain healthcare settings, or if it requires that the drug be dispensed to patients with evidence of safe use

conditions, then the REMS can provide and require the sponsor to have an implementation system. By requiring this kind of a system, we can require a sponsor to take reasonable steps to monitor and evaluate implementation of the elements by the healthcare providers, pharmacists and other parties to the healthcare system who are responsible for implementing the REMS.

According to the statute, the only required element is a timetable for submission of assessment of the REMS. Every REMS for a new drug application or biological license application contains provisions requiring the sponsor to periodically assess and submit a report of an assessment of the REMS to FDA. The statute specifies that the REMS must be assessed by 18 months, three years, and in the seventh year following approval of the REMS, although FDA can require more frequent assessments or eliminate assessments after it has sufficient experience with the REMS.

FDA is requiring each REMS to have measurable goals against which the sponsor and FDA can

assess the success of the REMS. And these goals and the metrics by which we'll assess the success of the opioid REMS will be discussed by other speakers.

Sponsors are required to submit reports of the assessments according to the time frames. And whenever we can, at the time that we approve a REMS, we're trying to describe in the REMS approval letter the types of data that should be collected and reported as part of the REMS assessment. And we'll undoubtedly be doing that as part of the opioid REMS.

The REMS requirements for generic drugs are a little different than what I've been describing for new drugs. And in the case of long-acting and extended-release opioids, there are already generic drugs on the market that will be required to have REMS. A generic drug sponsor may only be required to have a REMS if the applicable listed drug upon which its approval is based has a REMS. A REMS for a generic drug may include only a medication guide or patient package insert, elements to assure safe use and an implementation plan, and only if the listed drug has these elements. As I've already stated, if

there was a communication plan required for the listed drug, FDA must carry out the plan when a generic is approved. And generic drug REMS are not required to have a time table for assessment, although we can require them to assess it.

FDAAA states that for a REMS with elements to assure safe use, generics and the listed drug must use a single shared system to implement the elements to assure safe use or the generic sponsor has to obtain a waiver from FDA. Innovator and generic sponsors of isotretinoin has worked together even before FDAAA to create a single shared system so that the restricted distribution system that's in place doesn't unduly burden the healthcare system. And as you know, we've asked all of the sponsors of long-acting and extended-release opioids to work together in developing the REMS.

In conclusion, FDAAA provides FDA the authority to require sponsors to implement REMS when necessary to ensure that a product's benefits outweigh its risks. A REMS can include a variety of risk management tools. What elements of a REMS should be

required is a judgment call that requires balancing the need to manage the risks of the drug against the effects of the program on patient access and the burden of the program on the healthcare system.

DR. KIRSCH: Thank you.

Our next speaker is Dr. Rappaport.

DR. RAPPAPORT: As you've heard today, the FDA's spent a lot of time, effort and resources over the last 10 years to address the problems of the abuse and misuse of extended-release and long-acting opioids. However, you've also seen data today that clearly shows that the problems still exist and have worsened over time.

As a result, we've proposed this REMS as the next step to try and reverse these trends. You've just heard about the authority granted to FDA to require a REMS. With this new authority in mind, the agency began to consider whether a REMS could be implemented that would add to the efforts to reduce the misuse and abuse of extended-release and long-acting opioids. Early discussions included the pros and cons of requiring a REMS for individual opioid

products, various groups of products, or opioids in general.

By the beginning of 2009, our discussions had focused on the extended-release and long-acting opioids as the group of products that would be best suited to a REMS intended to address the problems of misuse and abuse of prescription opioids. Letters were sent to the manufacturers of these products notifying them that a REMS would be required. A meeting was then held between the FDA and the manufacturers of these products to discuss the design of the REMS and to propose that they cooperate to form a working group that would create a shared REMS for the entire class, including both branded and generic products.

The concept of a REMS was still fairly new in early 2009. Efforts were undertaken to inform and educate all stakeholders about REMS in general and the issues in developing an opioid REMS in particular, and a webinar was created in April of 2009.

The first opportunity for stakeholder input was at a meeting held in early May 2009 at which

stakeholders were invited to speak with FDA in order to express concerns, share ideas and ask questions. Members of the organizations representing prescribers, pharmacies and pharmacists, patients and patient advocacy organizations, medical education experts and insurance providers came to a series of meetings and provided valuable feedback.

Additional input from the public was obtained in late May during a two-day public meeting held to get input from any interested person who wished to comment on the REMS proposal, provide alternative ideas, or comment on how to minimize the burden of a large REMS to the healthcare system or on how to ensure continued access for patients.

The public was also asked to provide feedback on issues such as how restrictive the REMS should be given that a REMS can create burdens on patients and the healthcare system; how such a program could be implemented given the large number of patients, prescribers and other healthcare providers involved in the prescribing and dispensing of these products; whether existing systems such as those used

by pharmacies could be used to implement a REMS, and what metrics could be used to access the success of the REMS to demonstrate reductions in misuse and abuse and to examine any possible impact on patient access to these products.

A docket was then opened as another avenue for the agency to receive input from the public and stakeholders. FDA then reviewed the input in a process that took many months and that involved many people, as you've heard, from across the agency. The goals were clarified in order to set the stage for working groups which were formed to evaluate and analyze the input that we had received and then make recommendations regarding various elements of the REMS and the impact of those elements on patients and the public health.

The scope working group examined the pros and cons of limiting the REMS to the extended-release and long-acting opioid products or applying it more broadly to all opioid drug products. The access working group explored the potential for the REMS to limit patient access to the covered medications. The

pharmacy systems working group examined the currently existing pharmacy systems used for processing insurance claims and used for providing pharmacy records and printing labels to see how these existing systems could be used to manage a REMS that included patient, prescriber and pharmacy enrollment. The metrics working group researched the available databases that could be used to evaluate the effects of the REMS. There were also working groups for prescriber education, pharmacist education and patient education that examined methods for delivery of the educational components and how best to develop the content.

In December of last year, a public meeting was held with the manufacturers of the extended-release and long-acting opioids to hear about their progress in creating a REMS. FDA then held a two-day internal meeting at the National Labor College just down the street from our White Oak campus, and this meeting included all of the FDA staff that had been working on the REMS.

We reviewed the regulatory authority for

REMS, and then each of the eight working groups presented their recommendations. There were extensive discussions about the implications of all of the possible elements of the REMS, including the burden on the healthcare system and the potential impact on patient access. Considerations included the large number of patients and prescribers who use the products and whether to include all oral opioids or just the extended-release and long-acting opioids. A final proposal was drafted following which CDER and FDA senior management were briefed on this proposal.

The next presentation will describe the final REMS proposal from FDA. Our regulatory authority allows us to require a REMS. The intent is to require manufacturers to provide the means for prescribers to prescribe opioids safely, to select patients appropriate for the extended-release and long-acting opioids, and to instruct patients on how to use, store and dispose of these products safely.

The FDA's Safe Use Initiative is another resource that will be applied to improve the safety of the extended-release and long-acting opioids, and this

program will be described by Dr. Weiss. We will also continue to collaborate with and support the efforts of our federal partners and other nonfederal stakeholders. Thank you.

DR. KIRSCH: Thank you.

We will now have some time for some questions. My watch says that it's 11:35, and we will allow questions up until noon. We will start with those who got cut off at our earlier presentation. The first question is by Dr. Kerns.

DR. KERNS: This is for Dr. Conway from the earlier session. I guess I was looking for some good news in the data. It seemed to me that although there are increases in school-age reported use of prescription opioids, the increase is not as large as the general increase in availability of those medications. And I wonder if there is an opportunity for taking a look at what may be, if I'm interpreting the data correctly, some positive news in campaigns to promote awareness of teens and parents that may be realizing some benefit.

DR. CONWAY: So if I understand you

correctly, you're looking at the huge trend in availability or access and you're contrasting that to the rates of use among youth. And because the slope is not the same, you think that might be reflective of a change in the epidemic that might be due to some intervention. I think it's possible. We don't have good science to answer that question.

I think in part what you're seeing is a shifting in the landscape of drug use, which happens. Drug use increases and decreases for lots of different reasons. We've always known that availability has been inversely related to use. So it could be good news. Certainly, we're not seeing a continuing increase in rates of prescription drug abuse as we were five or ten years ago.

DR. KERNS: Can I ask a follow-up?

So a follow-up. I appreciate that, and I guess even from the SAMHSA presentation and so forth, we have a lot of effort going in to collecting data. And where we have a hint of some -- or we have a lot of efforts to try to promote education of youth and parents and our society more generally, we have few

data to evaluate their effectiveness. It's concerning to me that we're as a country expending a lot of effort already on this effort, and now we're considering further efforts today without really expending a similar amount of dollars to try to evaluate the effectiveness of the interventions that we have. And frankly, I don't want to represent myself as an effort, but it seems that the data that we do have don't strongly support continued educational campaigns and a lot of expenditure of money, that education isn't enough.

So if there's a hint here of benefit, it would seem important that NIDA, SAMHSA, and others expend effort trying to understand some of these data more thoroughly so that they could advise a group like this about any information that suggests that we're on the right track in some direction.

DR. CONWAY: Yes. Just to respond to that, I think in part the most effective interventions, and preventive interventions in particular, are those that are multi-pronged, and so simply providing information or knowledge about risks doesn't work. It has to be

done in multiple different levels, and those intervention programs that do that, that involve the community to identify what the risks are locally, the barriers to implementing them and then getting the community to adopt those preventive interventions according to plan is probably the most effective way to prevent. So I agree that simply transferring the knowledge is not sufficient.

DR. KIRSCH: Dr. Vaida.

DR. VAIDA: I have a couple questions. One for Dr. Governale.

On slide 6, when you were talking about the database, what it consists of, my first question is, does that also consist of mail order?

DR. GOVERNALE: No.

DR. VAIDA: No?

DR. GOVERNALE: Mail order is not included.

DR. VAIDA: Okay. And then on slide 16, there were two populations, one for immediate-release and one for long-acting opioids. And the first one did break out the dentist and emergency personnel. The second one didn't.

Do I assume those are just in other or were they really an insignificant number?

DR. GOVERNALE: The dentists and the emergency medicine were not among the top 10 for the extended-release opioids.

DR. VAIDA: Okay. And then I had one question for Dr. Dormitzer.

There was one slide that showed on where patients obtain medications, and I was wondering is there any data or information on patients like obtaining, actually getting it dispensed by physicians?

DR. DORMITZER: That data, I believe, was not collected.

DR. VAIDA: So this is just basically prescription data, that they got the prescription from the --

DR. DORMITZER: It was in response to their answering that they had taken a pain reliever nonmedically. And after responding positively to that question, they were asked how did you obtain your pain reliever. So it's the class pain reliever.

DR. VAIDA: Okay. So we don't know if it was dispensed by a provider compared to a pharmacy if a physician was dispensing the drug?

DR. DORMITZER: Well, they had reported that they either obtained it from one doctor or they had obtained it from a friend or a relative, and the friend or a relative obtained it from a physician.

DR. KIRSCH: Dr. Covington.

DR. COVINGTON: For Dr. Dormitzer, I'm trying to get a bit of a handle around what's underlying some of the use. Does the household drug use survey give any indication as to motivation for nonmedical drug use? In other words, how much of this is somebody gives their child Vicodin because they had a football injury versus same person taking the drug recreationally?

DR. DORMITZER: Well, but the question -- if you go to the definition of nonmedical use, that would say it was not prescribed for you and just for the experience it caused.

DR. COVINGTON: So it was all recreational?

DR. DORMITZER: It should be.

DR. KIRSCH: Dr. Wolfe.

DR. WOLFE: Two questions, one for Dr. Governale, one for Dr. Rappaport.

On the slide 13, where you are looking at unique patients receiving a dispensed prescription for ER/LA opioids, do you have that data broken down by individual drugs such as oxycodone, OxyContin, within that class? If you don't, is it possible to get it? Because it would be very interesting to see that.

Are those data available?

DR. GOVERNALE: Yes, actually, we do have that data available.

DR. WOLFE: Is it possible to bring it tomorrow if not today or anything like that? It'd just be interesting to see it.

DR. GOVERNALE: Okay. Sure.

DR. WOLFE: And the related question to Dr. Rappaport, Bob, I am excited by this REMS program for those drugs that really need to stay on the market, that we want to keep them, the benefits side and not the risks. You didn't mention, because I don't think it was part of your presentation at all,

the role of companies in undermining these. And, specifically, this is what the question is.

In 2001, you described the risk management program that you arranged with Purdue, and yet two years after that, the FDA found Purdue illegally advertising, over-promoting the same drug. This is two years after agreed upon risk management approach.

So my general question is, how does advertising, which can undermine and overwhelm the best intentions that we have for REMS, what role does that play? I mean, obviously, it's the manufacturer, and to some extent, the FDA in catching it. But can you just talk briefly about the role of advertising that actually increases the use of a drug, as certainly a lot of the campaigns of Purdue did.

Just how does that fit in?

DR. RAPPAPORT: Okay. It's not my area of expertise. We have a whole group of people in a separate division who actually have enormous expertise in this, but I'll tell you a little bit.

What we do is we attempt to craft the language in our labels as carefully as possible with

the help of the people in the Division of Drug Marketing and Advertising to be sure that the companies can only promote accurate information, what's known about the drug. Because basically, what's in the label is what they're allowed to promote and market based on.

So in the process of trying to address this issue, the label changes were intended, to a large degree, to prevent further episodes of marketing inappropriately for these types of products.

DR. WOLFE: Quick follow-up question, which is the standard, as you just said, for deciding whether it's a violation of advertising is does it comport with the label. And this incidence in January of 2003 was you had changed the label. The label was better, and the company was basically violating the label.

So the question is, having changed the label, done whatever you can on your side, what sanctions increased, if possible, can come down on those companies that illegally advertise and thereby clearly undermine a lot of the other elements that

we're trying to accomplish here?

DR. RAPPAPORT: I don't know if either Dr. Jenkins or Ms. Axelrad want to speak to that.

MS. AXELRAD: There are provisions in FDAAA that deal with direct-to-consumer advertising, and there are increased sanctions listed that can be imposed for violations of the provisions. If the committee would like, we could probably get a summary of those provisions to the committee.

DR. WOLFE: And doctor advertising as well or just direct to consumer?

MS. AXELRAD: Not my area. I know it deals with direct-to-consumer advertising. I'm not sure whether it went beyond that in terms of the new civil penalty authorities.

DR. WOLFE: It would be helpful to have that information for our discussion tomorrow. Thank you.

DR. KIRSCH: Next is Dr. Farrar.

DR. FARRAR: I have two brief questions, one for Mr. Boyd.

Could you give the committee a sense, if you know, about the number of physicians that actually

have now a certificate as a percentage?

Is he here? I guess not. Okay. We'll come back to that.

For Dr. McLellan, a question about some of the issues that you were bringing up.

I wonder whether there's been any thought given to the potential for advertising the use of safekeeping of the medication. You showed lots of open medicine cabinets, and at least in my practice, I require my patients to buy a safe in which to keep the medication in. I just wondered whether that had been considered and whether there was any attempt to think about that.

DR. KIRSCH: I don't believe either of those individuals are here.

DR. FARRAR: Okay.

DR. KIRSCH: Dr. Deshpande.

DR. DESHPANDE: I've got two questions on clarification. One can be for anyone of the four speakers, Drs. Governale, Dormitzer or Conway and Frank.

In the presentations this morning, the only

SES data that I saw was in Dr. McLellan's presentation. And what I'm wondering is the breakdown, where can we get the breakdown for either racial and socioeconomic status of the affected patients or the affected abusers in this whole problem. We've seen the age distributions but not the racial or the socioeconomic breakdown. The second question, I'll just pose it both at once. One's for Ms. Axelrad.

Under FDAAA, you mentioned the generic REMS and the limitations therein. Can BPCA or the PREA, the pediatric components, also help in defining the REMS for pediatric use when a company is looking for an extension of patent?

DR. KIRSCH: So let's take the second question first, and then give the others an opportunity to decide who's going to answer it.

Ms. Axelrad, will you be able to answer the question?

DR. AXELRAD: I'm sorry. Can you restate it?

DR. DESHPANDE: So the issue for me was the generic medications for children, a significant number

of medications we use are generic. And the two authorities that FDA has under BPCA and PREA, can they come into play so that REMS may be applied to some of the medications that are used for children?

MS. AXELRAD: The BPCA and PREA requirements operate independently of REMS, basically. Under the BPCA requirements, if we request pediatric studies in a drug, then they can get exclusivity. And under the PREA provisions, we can -- and, in fact, must require pediatric studies unless a company gets a waiver or a deferral. The REMS provisions in FDAAA are sort of operating in parallel and completely independently of those provisions and would apply to whatever population of patients for which the drug is approved, basically.

DR. KIRSCH: And Dr. Deshpande's first question, is anyone able to answer that for him?

DR. DESHPANDE: So it's the breakdown of ethnicity and socioeconomic status in the presentations this morning. Clearly, we don't have those all today, but where can we get those?

DR. KIRSCH: Dr. Dormitzer.

DR. DORMITZER: Well, DAWN does collect age, sex and race but does not collect SES. But I don't know how I would -- in terms of ratios, I'm not sure how I would do that analysis. But SES is not collected with DAWN.

DR. KIRSCH: Thank you.

Dr. Bickel.

DR. BICKEL: I have a question for Mr. Reuter.

Dr. Gallagher in his presentation earlier today suggested that those patients not involved in structured programs may be more likely to be involved in diversion. And I was wondering if SAMHSA had any information about individuals receiving buprenorphine are also receiving psychological or other counseling.

MR. REUTER: The quick answer is we have limited data. Congress tasked us. It's actually required that we do an evaluation study that evaluated whether or not physicians getting these buprenorphine waivers were providing effective treatment. The only we could do that was to survey them and ask them how often they provide counseling, and a lot of other

things, too.

The results were a little bit dismaying, to say the least, that the vast majority provided counseling or saw that their patients got counseling and other kind of services maybe twice every 30 days. So that's the best we can do. We do plan to do more work on that in the future.

Just in answer to one of the other questions that I heard, you mentioned what was reported in the National Survey on Drug Use and Health, whether that nonmedical use was entirely recreational. And the answer is no, that some of those people use it nonmedically. One of the criterion is that they used it without a prescription.

Now, some people might argue that the specific scenario you described, which is a parent gave it to a child who had a football injury, some people may question whether that's recreational use or a different kind of a medical use. So I wanted to just address that.

The issue posed to ONDCP about educating people on proper storage and disposal, there's

actually quite a bit going on on that, particularly on the disposal. Drug take-back programs are very active, and there will be formal nationwide drug take-back programs in the near future. Part of that is to get that unused, unnecessary medication out of the medicine cabinets and safely disposed.

DR. KIRSCH: Dr. Carter.

DR. CARTER: Yes, I had two questions. The first was a follow-up to Dr. Covington's question to Dr. Dormitzer. And that is, given that the definition for nonmedical use includes drug not prescribed for oneself, is it possible from the data that we have to determine when drug was used without a prescription with a therapeutic intent from those cases in which it was not?

DR. DORMITZER: I don't believe that NSDUH collects that information.

Is there someone from SAMHSA that could --

MR. REUTER: You're correct. It does not.

DR. DORMITZER: Yes. It's not collected.

DR. CARTER: The second question was for Dr. McLellan, so if he's not here, I'll hold on to

that.

DR. KIRSCH: Dr. Nelson.

DR. NELSON: Thanks. I have a question for Mr. Reuter and one for Dr. Governale.

For Mr. Reuter, although the buprenorphine education program evaluation that you had showed by Lofwall showed knowledge retention, this is not particularly high level learning. I guess the question is, did it show any practice or outcome change? And related, did the entire program, which is a somewhat ambitious program, does that whole program actually show or suggest success?

MR. REUTER: The answer to the first question does it clearly show a change in practices, and the answer is no. It just showed that something was actually learned. And the second question was the entire buprenorphine program itself, whether that can answer those kind of questions. And the answer is no, it cannot. We don't have that kind of analysis to date.

DR. NELSON: Yes, thank you, because that's a fairly more aggressive program than perhaps we're

thinking about moving forward.

For Dr. Governale, on slide 19 in your presentation, the most common reason to switch to an extended-release or long-acting opioid was that it was, quote, "ineffective." And I'm not sure what exactly the term "ineffective" means in that context. Among the things it could mean was that the immediate-release just didn't work, which would be probably a poor reason to change to an extended-release form, or maybe the immediate-release was needed at too high a dose. It was no longer effective, and they needed more drug.

So is there any insight to that?

DR. GOVERNALE: Well, this was a free text form where the physicians are filling out the reasons why they would be switching to an extended-release opioid. But the meaning that I would glean out of ineffective was that whatever medication they were on previously was not treating the pain adequately.

DR. NELSON: I'm sorry. So it wasn't always an immediate-release opioid, it could have been anything else?

DR. GOVERNALE: Correct, it could have been --

DR. NELSON: So they could have gone right from a nonsteroidal to an extended-release?

DR. GOVERNALE: Correct. Oh, no. It was among the opioid class. It could have been either an opioid of any --

DR. NELSON: So it could have been another extended-release opioid?

DR. GOVERNALE: Yes.

DR. NELSON: I see. Thank you.

DR. KIRSCH: We have a very long list of individuals who've asked to ask questions. Unfortunately, we're going to have to cut off the questions at this point. I'd strongly encourage presenters from today to make all efforts possible to be here tomorrow when there's further discussion.

Right now, we're going to take an hour break for lunch. We'll reconvene again in this ballroom in 60 minutes, which will be 1:00. Panel members, please remember that there should be no discussion of issues at hand during lunch amongst yourselves or with any

member of the audience. Thank you.

(Whereupon, at 12:00 p.m., a luncheon recess was taken.)

A F T E R N O O N S E S S I O N

DR. KIRSCH: We will re-begin the meeting Our next speaker is Dr. Rappaport.

DR. RAPPAPORT: Okay. Good afternoon. As you are trying to digest your lunch, we'll go into what we've actually proposed in the REMS and why.

So the elements of the REMS that we are proposing, after much discussion, analysis and evaluation, include a medication guide, elements to assure safe use for prescriber education, mandatory sponsor-developed patient education materials made available to prescribers for voluntary use with patients. And there are a number of things that we had put into our original straw man back over a year ago that we are not going to include.

We are not requiring enrollment of any individual prescribers into a REMS program, we're not requiring real-time electronic verification of prescriber training at the pharmacy level, and we're not requiring a communication plan. It should be noted with a communication plan, based on the statute, that any such plan would have to be implemented by FDA

because there are generics for some of the long-acting and extended-release Schedule II opioid products. That is a resource issue for us.

These were the goals that we defined for the opioid REMS for the long-acting and extended-release products. To reduce serious adverse outcomes resulting from inappropriate prescribing, misuse and abuse of long-acting and extended-release opioids while maintaining patient access to these medications. Adverse outcomes of concern include addiction, unintentional overdose and death. And I urge you to pay attention to that last sentence because that really clearly defines why we carved out the class we did.

This will be accomplished by educating prescribers in appropriate patient selection, dosing and patient monitoring and by educating patients in the safe use, storage and disposal of opioids.

We are recommending against broadening the scope of the REMS as some have proposed to include all Schedule II opioids. The long-acting extended-release Schedule II opioids present a unique risk to patients

related to their formulations and pharmacokinetics, and they represent a significant and growing problem of serious adverse events in patients and others when not used properly. In other words, this class of opioid products is the group of products that is resulting in most of the overdoses and most of the deaths when adjusted for usage.

While the immediate-release Schedule II opioids clearly present serious risks to patients as well if not used properly, one other issue for us is that broadening the REMS to include all agents would be difficult to justify and would create a greater burden on the healthcare system.

Two other reasons to consider in this decision were that for each product, we would have to define new safety risks that had occurred in order to include them in a REMS, and because we believe that the existing educational program that we are proposing will actually cover prescribers of the immediate-release Schedule II and Schedule III opioid products. Because as you've seen, the majority of DEA registrants have a Schedule II registration and are

probably, for the most part, prescribing both groups of drugs. So we will capture them in our educational program.

The broader problem of misuse and abuse of immediate-release Schedule II opioids and lesser opioids is really more appropriately addressed, however, by the Safe Use Initiative and by actions of other federal agencies.

So the proposed element to assure safe use in regard to prescriber training, FDA is proposing that sponsors be required to develop an educational program that would educate prescribers about appropriate patient selection, dosing and patient monitoring. Prescribers would also be trained to counsel patients on the safe use, storage and disposal of opioids.

We will encourage that the training be developed in partnership with an appropriate independent third party such as the Federation of State Medical Boards. And another key message here today, there's been a lot of misconception about this. We have the final say in the content of the training.

We will have complete oversight over that training, and we will make sure that it is appropriate, that it's not in any way biased or inadequate.

Even though prescribers would not be required to demonstrate evidence of training to prescribe these products, the sponsor will be required to demonstrate that prescribers have been trained and that knowledge of appropriate use has improved via surveys of the prescribing community. And sponsors will also be encouraged to explore appropriate incentives such as CME credit to encourage prescribers to undertake the training.

At this time, we're not recommending individual enrollment of prescribers into a REMS program or real-time electronic verification of prescriber training at the pharmacy level. This would be extremely burdensome to the healthcare system, as we heard from many sources over the past year. And as you heard today, there are currently -- this number's increased clearly -- over 1.3 million DEA registrants. Approximately 700,000 are prescribers who may fall under the REMS program.

A requirement for individual prescriber registration and real-time verification of training could create a balloon effect with some, perhaps many, prescribers opting out of the program with potential adverse consequences to access to pain medications. One of the goals of the REMS is to maintain access.

In the long term, linking education to the existing DEA registration system would be more efficient, but it would also require legislation.

We discussed at length whether there should be exemptions to the training requirement for certain prescribers. And I'm not sure we fully resolved this. We do agree that if there are exemptions, they should be very limited and based only on verifiable credentials such as board certification in pain medicine.

FDA believes that exemptions should not be based on the practice location such as inpatient versus outpatient since prescribers in all settings need to understand how to use long-acting and extended-release Schedule II opioids properly.

We acknowledge the limitations of Med

Guides. We know that they're not always given out, but they are one way to try and reach patients and to educate them under the REMS. So these will be required for each long-acting and extended-release Schedule II opioid. We could include a class language along with product specific information. The final decision on whether to have individual class or groups of different types of Med Guides has not been made.

We also are asking that the sponsors are going to be required to make patient education sheets available to prescribers and that they'll be encouraged to use those in counseling their patients. The content again would be FDA approved, and we're looking at a one-page tear-off sheet, not anything extensive, obviously, and language appropriate to the patient population.

In regard to pain treatment agreements or patient/provider agreements, we're not going to require those under the REMS. But Dr. Weiss will be talking later about how under the Safe Use Initiative we'd like to partner with other stakeholders who have an interest in those to make the existing models more

broadly available for voluntary use.

At this time, we're not recommending individual enrollment of patients in a registration system. These again would be very burdensome to the healthcare system and create a stigma for pain patients that could adversely affect patient access to their medications. There are nearly 4 million patients prescribed long-acting or extended-release opioids annually, and enrolling that many patients in a registration system would be an enormous undertaking with very unpredictable effects on access.

So overall, it's important to note that we will be carefully monitoring the effects of the program, and if it doesn't seem to be working or it seems to be having negative impacts, we will consider making appropriate changes.

Again, Dr. Weiss will be talking about this at some length, but we do propose that under the Safe Use Initiative, we engage with partners to initiate broader efforts to address the problems of misuse and abuse or prescription opioids. One proposal would be for government-sponsored or endorsed website that

would contain information for patients and others on safe use of these products, but there are a number of other potential proposals that Dr. Weiss will be discussing.

So in summary, what we're recommending is a three-pronged approach. First, we'll require REMS for all long-acting and extended-release Schedule II opioids. That will include required prescriber training and patient education. We'll engage in safe use partnerships to achieve broader goals that do not fit well under the FDA's REMS authorities, and we will continue to work with federal agencies to address the problem via alternative strategies.

DR. KIRSCH: Thank you.

Our next speaker is Dr. Mary Willy.

DR. WILLY: Good afternoon. I'm Mary Willy, and I'm from the Division of Risk Management in the Office of Surveillance and Epidemiology in CDER. I am the lead of the metrics working group, and I'm going to present a summary of our work on the metrics for evaluating the opioids REMS program. Today, I'm going to review the goals of the opioids REMS, which you've

just heard but I'll repeat again; summarize the proposed metrics; discuss the challenges that we've identified; and then share some conclusions.

So here again, I'm repeating the goals. When we began to work on the metrics, we recognized that it's very important that you have the goals identified for the program. So the goals for the opioid REMS are to reduce the serious adverse outcomes resulting from inappropriate prescribing, misuse and abuse of long-acting and extended-release opioids while maintaining access to pain medications. The adverse outcomes of concern would include addiction, unintentional overdose and death.

In addition to identifying the important metrics, which I'll talk about shortly, the working group made a series of recommendations. The group recommended that we would utilize multiple metrics and data sources to measure the impact of REMS. We would create new data sources to measure certain components of the REMS, including surveys and surveillance systems. We would measure the impact of the REMS on outcomes related to both extended-release products and

all opioids.

We also recommended that we would establish working definitions for the outcomes of interest. We would establish baseline metrics to determine the degree of the REMS changes and knowledge, behavior and health outcomes, and we would account for the interventions that had been initiated by other organizations in ongoing trends in drug abuse.

This diagram summarizes the data needs that the working group identified. The needs were separated into three categories, knowledge, behaviors and outcomes. Although the specific components of the education efforts are not finalized, the working group anticipated the knowledge metrics will include measuring the patient understanding of safe use, safe storage and proper disposal of opioids. And for prescribers, the knowledge metrics needs will include measuring the understanding of the need for patient counseling, proper patient selection, dosing and patient monitoring.

The behavior metrics would include measures of inappropriate prescribing, a challenging metric

that needs to be developed and nonmedical use.

Outcome metrics would include serious outcomes such as overdose, addiction, hospitalization and deaths. Metrics that focus on access to care also fall into this category.

I'll now review the proposed metrics and describe some of the proposed databases that haven't been discussed this morning. So first of all, as with many REMS, we will need to develop some process metrics to determine if the elements of the REMS are working. Since the opioid REMS include prescriber education, there will be a need to collect training data. The procedures for collecting this information will need to be developed once the details of the REMS are finalized.

Surveys are the primary tools used to monitor prescriber and patient understanding of important safety messages. Surveys provide us with prescriber- and patient-level data. As with all other REMS, these surveys are implemented by the sponsors. And so the sponsors for the opioid REMS will need to collaborate on funding and data collection for this

metric.

The most challenging set of metrics to monitor are those related to inappropriate prescribing. Since the goal for opioid REMS is to reduce adverse outcomes related to inappropriate prescribing, the working group thought these metrics would be very important. The metrics might include looking for prescribing of certain opioids to non-opioid-tolerant patients, looking for prescriptions to certain types of patients, for example, those with acute pain.

The working group proposes using prescription claims databases to identify these type of prescribings. These data are very timely, but the findings will be limited to some extent since there will not be medical record validation.

To help us understand the possible options for identifying inappropriate prescribing, FDA initiated a collaboration with the Center for Medicare and Medicaid Services to conduct a small pilot study looking for prescription to nontolerant patients, non-opioid-tolerant patients, and markers of concerning

patient behavior such as increased use of different prescribers and pharmacies and early refills, although it is not clear if these markers of patient behavior can help identify changes in prescriber behavior.

Nonmedical use and abuse will be monitored using NSDUH, a database that you heard about this morning. The data are nationally representative but are not all publicly available and may not be timely. Other databases may also be used.

Unintentional overdoses can be monitored using two databases, the National Electronic Injury Surveillance System Cooperative Adverse Drug Events and the National Poison Data System. These data are nationally representative and provide some drug-specific information. The data are not all publicly available and in some cases, may not be as timely as we would like.

In my next slides, I'll provide a little information about these databases. So NEISS-CADES is a database that's sponsored by CDC and FDA in collaboration with the Consumer Products Safety Commission. The database identifies emergency

department visits that are due to unintended adverse events from medications. NEISS-CADES provides updates once a year usually nine months after the end of the previous year.

The National Poison Data System is maintained by the American Association of Poison Control Centers. NPDS collects information from 61 poison control centers. The exposures are classified into a number of groupings that reflect unintentional use, therapeutic error and abuse. The data are not all publicly accessible and will require special funding.

Another database that collects information on emergency department visits is DAWN, a data system that was discussed this morning by Dr. Dormitzer. These data are nationally representative and can be drug specific. The data are available 9 to 12 months after the end of the previous year.

Changes in the number and rate of admissions to treatment programs can be monitored using the treatment exposure database. Admissions for treatment will be used as a proxy for a measure of changes in

addiction. The data from TEDS are nationally representative and do provide some drug-specific data but not as timely as we would like. TEDS represents data from over 10,000 facilities in the United States and provides, as I said, some specific opioid data from a sample of states.

The number and rate of death from opioids will be monitored using information collected from the National Vital Statistics. The data are nationally representative and have some information on the class of drugs but are not timely. We'll be hearing more about this data system from Dr. Anderson.

Changes in access to opioids will be monitored using the Medical Expenditure Panel Survey or MEPS. This is a program that's funded by the Agency for Healthcare for Research and Quality. This survey includes questions that gather information on access to care, although the data are delayed by two years.

Using MEPS, we plan to look at the patients who report moderate to severe pain who say they could not get a prescription and explore the reasons

reported for the lack of access.

The working group identified a number of challenges to the evaluation plan. First of all, it'll be difficult obtaining timely data in some cases. Most systems do not collect drug-specific data. Most data will be population level and not patient level. Small changes will be hard to find. And there are many other efforts that have been initiated, and so it will be difficult determining which changes are related to the opioid REMS.

As mentioned just previously, there are going to be lags in obtaining data from certain data systems. This slide shows for you a schematic of what we anticipate for the information that we may be collecting in the first year post REMS. So data will be available 18 months after the initiation of the REMS in some cases, although the process data and perhaps information on the knowledge metrics may be available sooner.

As we move forward, FDA plans to work with a number of partners to develop new methodology. I've already discussed the pilot study that we've initiated

to look for inappropriate prescribing. We're working with the CDC to develop our methods to identify unintentional overdoses using the NEISS-CADES system, and we're exploring other possible collaborations with the Veterans Administration and Department of Defense as well as the state prescription monitoring programs.

In conclusion, I'd like to emphasize the following. We know there are many data sources that area available that can help us. None of them is specifically tailored to measure the outcomes of the opioid REMS. The roles and responsibilities across multiple sponsors and the FDA will need to be determined. The sponsors will be responsible for funding and implementing the REMS as well as the final evaluation of the REMS.

Finally, I'd like to acknowledge the other members of the metrics working group who worked with me very hard on developing our recommendations. Thank you.

DR. KIRSCH: Thank you.

Our next speaker is Dr. Paulozzi.

DR. PAULOZZI: My name is Len Paulozzi. I'm

a medical epidemiologist with the Injury Center of the Center for Disease Control and Prevention, and I appreciate the opportunity to address this advisory committee meeting today.

Most of my work in the past has had to do with drug overdoses related to pharmaceuticals such as the West Virginia study that was talked about earlier today. But my charge today was to talk about the use of prescription drug monitoring program data in addressing the impact of the REMS.

I thought that from my perspective, the highest priority methods for surveillance of REMS impact included (inaudible, cell phone noise) -- including these three things: prescription drug monitoring program data, medical examiner data from states with state medical examiners and PDMP, and DAWN emergency department data. I'm just going to talk about the first and the second this afternoon.

First, I'll give you a background on PDMPs, some of the advantages and disadvantage of PDMPs, the standard data elements and suggested metrics that could be developed from PDMPs for tracking opioid-

related outcomes, in particular, the health outcomes.

The advantages of prescription drug monitoring programs are that they include a high level of drug detail, including the formulation, the prescriber and dispenser identifications. Information comes from the prescriptions that are written on controlled substances in the state, which are sent to a centralized database within each state. So basically, the information is what you find on a standard prescription form.

The timeliness of prescription drug monitoring programs is better than most other data sources. The other advantage, of course, is that prescription drug monitoring programs have been ongoing in some states for 40 or 50 years, other states for a few years. So in most states, we will have a baseline of at least a couple of years of information already collected.

We're talking about millions of prescriptions here for controlled substances and for opioid analgesics. So the statistical power is there. There are large enough numbers to detect small

changes. We're talking about basically recording all the prescriptions for controlled substances in a given state, which makes it a population-based dataset, at least for prescriptions dispensed in a state, and it allows the use of prescriptions as a denominator for the calculation of rates.

Because the data is collected over time and personal identifiers are collected for the providers, the pharmacists as well as the patients, you can link up all the prescriptions for an individual. You can link all the prescriptions written by a given prescriber and dispensed by an individual pharmacist. So you can look longitudinally at the patterns and the frequency of prescribing by individuals and the frequency of filling prescriptions by patients.

The cost would be limited to processing data that is already been collected in states for reasons that originally led to the establishment of prescription drug monitoring programs, which was the prevention of diversion of controlled prescribed drugs.

One additional advantage is that the Center

for Excellence in Prescription Drug Monitoring Program located at Brandeis University is in the process of currently establishing an independent, de-identified PDMP database with data from all states that are legally able to share their data for research purposes, and this data would be made available to FDA for evaluation of the impact of the REMS.

I spoke earlier of timeliness as being an advantage of PDMPs. This is information from the Alliance of States with Prescription Drug Monitoring Programs in a recent survey of its membership. Some 33 PDMPs responded to this survey. Among that group, 16 or about half required reporting by pharmacies on a weekly basis of prescriptions. Three required daily reporting by pharmacies. So we're talking about more than half requiring weekly reporting. And, in fact, some of the states that currently or at the time of the survey were asking for monthly or biweekly reporting are moving rapidly towards requiring weekly reporting by prescription drug monitoring programs.

There are some disadvantages, to be sure, in using PDMP data. There is no national compiled

database. There's work ongoing to try to aggregate data among multiple prescription drug monitoring programs. But as of now, we are talking about a sample of states or a subset of states, which may, in fact, cover a large percentage of the U.S. population. But we probably will not have a national complete database. Not all states, in fact, yet have prescription drug monitoring programs.

The identifiers are probably not shareable outside of the state, which would require using the state's linkage of patients' and doctors' prescriptions. So the state would have to see how many prescriptions an individual had, how many prescriptions a doctor wrote.

The accuracy of the state linkage methods needs to be assessed. States currently link prescriptions for an individual when a doctor calls and says I want to report on a patient. They tell them how many prescriptions this patient had within the past six months or a year. The methods they use vary from state to state, and there has to be some work done to validate the completeness and accuracy of

that linkage.

PDMPs don't typically capture methadone from opioid treatment programs. They do capture methadone when it's prescribed for use in pain and dispensed at pharmacies.

There undoubtedly are other practical, technical and legal challenges to using this data as a surveillance source. It was originally designed for another purpose, but it has advantages for the purpose at hand today.

I said that not every state has an PDMP. As of last week, when the governor of Delaware signed the prescription drug monitoring program, there are 44 statutorily authorized PDMPs in the United States. And this graph shows the growth of PDMPs beginning in 1939, which I think was California, slow growth up until year 2000, whereupon federal funding from Harold Rogers and the NASPER grant program, that has been mentioned earlier, basically dramatically accelerated the adoption of PDMPs. I think also the problems with controlled substances helped to motivate some states to establish them. But as of now, we are looking at

44 states.

This shows you the states that are not included as of yet. They're shown in black, Montana, Nebraska, Missouri, Arkansas, Georgia, Maryland. District of Columbia is not included and New Hampshire also does not have a program. States shown in blue are new states where the program was passed but it is not yet operational. So you can see that most of the large populous states in the country are in the system, and some of the less populated more rural states are not.

I spoke about data elements. This basically summarizes the data elements that are currently listed as in the model act that the state PDMP organization is promulgating. For the prescription, the database would include information on the prescription number, the date issued by the prescriber, the date is was filled, whether it was a new prescription or a refill, the number of refills written, and in some states, there's a state-issued serial number on the prescription, and that would be captured if it's there.

Drug information includes the national drug code, code for the drug; the quantities dispensed; the days supplied, dispensed. For the patient, there's an identification number. In some states, that may be the driver's license number. The name of the patient, the address, date of birth, sex, source of payment, and the name of the person who receives the prescription if it's other than the patient.

For the prescriber, it's the identification number and the dispenser identification number, which the states can use by linkage to other databases to identify the individual provider and identify their specialty and so on.

There's a lot of standardization of data elements. There is some variation in serial numbers and so on among states, but basically, this is the list that they are gathering.

So now I'm going to turn to some suggested metrics, the measures, statistics that might be developed from use of the prescription drug monitoring program data. I'd have to say that there's a lot of work that needs to be done in terms of evaluating

sensitivity and specificity of these measures. But in general, most of these metrics that I'm talking about are associated with an increased risk of dying of a prescription drug overdose. I know that from an unpublished study that we're doing now in the state of New Mexico showing increased risk of drug overdose with patients who show these various metrics. So it's possible to generate these with the data elements that I talked about. It's just that most PDMPs are not in the habit of doing this as of yet. But for most of these, we have already generated them using PDMP data from New Mexico, so I know it's in practical terms possible to do.

So in terms of provider education, one of the areas that Mary indicated an interest in, you could look at the median starting dose for each opioid. You have the type of opioid. You have the dosage on the prescriptions. You could look and see how that has changed over time. You look at the median daily dose for patients. You could look at dose escalation.

For example, a critical drug in this area is

methadone. The idea is to start low and go slow with methadone. And then you can develop metrics. There's a paper by White published in 2009 which defined dose escalation as 50 percent increase or more in dosage each month for two consecutive months. There are various ways this could be done. This is just one suggestion.

You could look at the percent of patients for whom providers requested PDMP reports to look at the penetration of the PDMP to see how often providers are adopting that, how well is provider education working. And part of the education would be to tell them to check PDMPs before prescribing and during prescribing, and the percent of the providers in the state who are actually requesting reports, not those registered but those actually requesting reports. Those statistics have been relatively low in terms of percentage of providers requesting reports so far.

Other metrics could be developed for inappropriate prescribing. Median daily dose in patients with no opioid prescriptions in the previous three months, no tolerance; lack of continuation of

drugs that are really intended for continuous, around-the-clock dosing; disproportionate share of doctor shoppers or pharmacy shoppers in a doctor's practice by specialty type; the combination of opioids, especially methadone with benzodiazepines. Benzodiazepines are Schedule IV, and they're tracked by almost every PDMP in the United States now.

So you could look at opioids combined with benzodiazepines. You could look at inappropriate drugs given to children or the elderly. You have the patient age. You have the types of drugs.

Metrics for misuse, abuse or addiction, you could look at trends in and differences among drugs in the proportion of patients who are meeting doctor shopping or pharmacy shopping definitions, whatever those are determined to be, more than X number of doctors per six months or per three months or per year, more than X pharmacies in a time period. You could look at differences among drugs in the percent of the time that you find early refills or overlapping prescriptions for the same drugs shown to be in other studies a risk factor for misuse.

Also look at high daily dosages. Morphine equivalence of opioids could be calculated for patients. You could add up across all their drugs. You could look at their peak daily dosage. Some guidelines in some states talk about peak daily dosages as an indication for referral to specialists. And there's one study in Group Health which shows opioid daily dosages of more than 100 morphine milligram equivalents per day associated with a sevenfold increase risk of a serious overdose event. So there's some validity behind a lot of these measures.

Suggested metric on effects of inappropriate use, you could look at -- the question here is, is the REMS having an adverse impact on the appropriate use of opioids, to be put it in other words. So you could look at the change in the prevalence rate of patients treated with opioids by different numbers of providers or going to different number of pharmacies and look at -- the most desirable impact would be concentrated in the group with multiple providers and presumably, hopefully, less impact in the group who have a single

medical home for prescription of their opioids.

You could look at the changes in prescription rate among persons over 75 or more years old. It's a group with a very low drug overdose rate. It's a group that reports very low rates of prescription misuse and abuse. In theory, there should be relatively little impact of REMS on use of opioids in this group.

The other way to use this data, as I started out by saying, is combining it with mortality data. And in particular, I'm talking about mortality rates from medical examiner, and in particular, statewide medical examiners who can give you all the overdose in a particular state.

You can look at deaths caused by a particular drug because the MEs do report particular drug outcomes per hundred thousand prescriptions for that drug or per hundred thousand morphine equivalence of a given drug to compare across drugs. This wouldn't work, of course, for opioids with long-acting and short-acting forms such as oxycodone. Medical examiners tend to know that it was oxycodone and don't

always know the formulation of the drug that was involved in the drug overdose; was it immediate-release or extended-release? And the same issue with methadone. They may find it in the decedent's body but not know whether it was a prescription methadone or methadone obtained from an opioid treatment program.

You could also look at decedents with a record in the PDMP for a drug per how many of those there are per 100,000 prescriptions for a given drug. And lastly, you could look at the interval between the prescription and death, which is though to be an important measure in overdoses related to methadone.

Just to give you a picture of how common this is that you have both state medical examiners and PDMPs in the same states, there are 21 states with state medical examiners listed on the left. The asterisks actually show the states with state medical examiners who are enrolled in the DAWN medical examiner surveillance system. But of these 21 states, only five of these lack prescription drug monitoring programs as of May of this year. So there are 16

states that have both PDMPs and state medical examiners, and they might become willing partners in terms of monitoring the impact of the REMS. Thank you.

DR. KIRSCH: Thank you.

The next speaker is Dr. Anderson, and I'd like to remind the speakers to either leave their cell phones and BlackBerries and iPhones and so forth at their chair or turn them off when they come up to the podium.

DR. ANDERSON: Good afternoon. My name is Bob Anderson. I'm chief of the Mortality Statistics Branch at CDC's National Center for Health Statistics. And as such, I'm responsible for the compilation and publication of national mortality data and statistics.

I'm going to talk a little bit today, as Dr. Willy mentioned, about sort of some of the challenges associated with the mortality data and how these might be used to help sort of track progress with regard to opioid deaths. And she mentioned that timeliness was an important problem with the mortality data.

Just to give you some context, we just released in May our data for 2007, and here we are halfway through 2010 now and we have 2007 data. So timeliness is certainly an issue. And I'll talk a little bit about why that is and give you some idea of how we collect these data, and then also, some of the things that we're doing to sort of address these issues.

I also want to talk a little bit about cause of death quality because that obviously is an issue whenever you're looking at a specific cause of death. In this case, we're talking about opioid-related mortality.

The National Vital Statistics System is really not a national system, per se. We do collect all deaths registered in the United States, so in that sense it is a national system. But the registration of deaths is not sort of a federal function. This is done in the states and territories. So we're collecting data from 57 registration areas totally, all 50 states, the District of Columbia. New York City has its own separate registration area for births

and deaths, and then five territories.

You can imagine when you're dealing with different state systems, you're going to have issues related to the collection of the data. We've had this relationship with the states for a long time. The vital statistics system in the United States stretches back about 100 years. And so we do have generally consistent data coming from the states. We have standards in place, but nevertheless, we do still have issues in collecting the data in particular.

So the big issues we have is that our national reporting, our national file, can only be released as fast as our slowest registration area sends in the data. Now, part of the reason why some of these states are really slow is that this is still largely a paper-based system. This is changing, though. There are electronic systems that are being developed, and I'll talk a little bit about that a little more as we go through here.

The information that's collected, we have demographic and some personal information about the decedent. This is typically reported by a funeral

director. And here, we're talking about information like age, race, sex. We have education, marital status, some information about their geographic residence, that sort of thing. And this is typically reported by a funeral director usually based on information that they obtained from an informant who is usually a close family member, or at least we hope it is usually a close family member.

Then we have the cause of death as well. And natural deaths are typically reported by an attending physician, although that can vary. Sometimes it's sort of the intern or sort of the low man on the totem pole so to speak that ends up getting that duty.

The accidental violent deaths are typically reported by a medical examiner or coroner. And the medical examiner or coroner systems are quite diverse in this country. As Dr. Paulozzi mentioned, about 21 states have state medical examiner systems. These are centralized systems where you have fairly consistent investigation and reporting going on. Many of the other states have decentralized systems and some sort

of mixed medical examiner or coroner systems, and things can be quite inconsistent as a result.

So to focus it a little bit on timeliness here, timeliness has actually gotten worse over the last several years. And in part, this is because of problems with funding and state budgets. I don't know if many of you know that some states have actually had to furlough some of their employees recently, and this is happening in the vital registration offices as well. And, of course, this is causing us problems because they're getting slower.

Also, the development of electronic systems have actually contributed to this in a way. We've found that as a state implements an electronic system, their timeliness actually gets worse, particularly in that first year of implementation, as they work out the bugs with their system, but then things tend to get much faster. The problem is that these states are not implementing these systems all at the same time. They're doing it incrementally.

So this kind of gives you an idea here where we're at in terms of timeliness. We typically publish

our data in two forms. We publish a set of preliminary statistics, and then later once we have all of the data, we publish our final statistics along with the final data file. The yellow line here gives you the timeliness for the final data and the red line for the preliminary data, and you can see that the trend since 1995 is upward towards more time from the end of the data year.

So you can see there in 2007, we were just over two years from the end of the data year. And in 2008, it looks we'll probably be in about the same position. But I'm going to talk a little bit about what we're trying to do to reverse this trend.

Now, electronic death registration, I think, has the greatest potential to reverse this trend, although I mentioned earlier that we do have problems, particularly in the first year of implementation. We can really dramatically improve timeliness with these sorts of systems once they're implemented and mature and have sort of disseminated themselves throughout the states.

There are also some issues related to

security. This can help us with linking births and deaths, and I won't go into that because it's not particularly relevant here. And also, it can help us with disease and pandemic surveillance. In this case, I think we're talking about today, about opioid mortality surveillance, and so it can help us with that.

The systems are currently functioning in about 24 states, D.C. and New York City, so 26 registration areas total. And here's a map that kind of shows you what the coverage looks like. So the green states all have systems that are functioning, well, more or less functioning. In some cases, these systems are functional but nobody is using them, and so we do have a problem there. I know in one case, the system is there and functioning, but they can't get any data out of it because of some problems with the contractor.

Then most of the other states, while the systems are functioning, they have less than 100 percent coverage. So we're looking at a state like Utah, for example, which has a very nice system.

They're registering I think 65, 70 percent of their deaths all electronic, which is actually pretty good compared to some of the other states. Texas is up to now about 50 percent of their deaths. Only a couple of states are really 100 percent electronic, New Hampshire. California, they claim to be 100 percent electronic, although not all physicians are using the system. They've got sort of a work-around to help their physicians get their data into the system. But it seems to be functioning quite well. We do still have a few states that haven't done anything, and we're hopeful that they'll be able to get into the game here in the near future.

Well, we did a pilot with New Hampshire. We've been working with them over the last year to try to see what's possible in terms of timeliness, and they're actually sending us data in a very timely fashion. The data that we're getting is on average coming to us within about four days from the date of death, which is very fast. Now, this includes the cause of death, but it does not include coded cause of death. So we sort of have to cull through it using

sort of text strings and things like that. Now, there are other states as well with systems that are reporting an ability to transmit data within a week, and we'll sort of expanding our pilot to include many of the other states here in the future.

We have a new contract with the states that's coming available here. I think it will be effective for 2011, assuming all goes well. We do have some timeliness goals that are associated with that contract. At this point, regardless of whether the state has an electronic registration system or not, the contract will require them to provide the mortality data, including the cause of death, within 25 days of registration, which is way more timely than what we're getting right now. So we were happy to sort of make that compromise. But we expect that the EDR states will be much faster, and we are going to be expanding our surveillance pilot to include as many EDR states as we can get, and these will be expected to deliver their data in five days.

Now, I did want to say something about cause of death certification and the challenges. The

physicians, and even in some cases medical examiners and coroners, although not nearly as often, they don't understand why the cause of death on the death certificate is important. They don't realize that this information is actually used for something, for public health purposes. And so we occasionally get useless information on the death certificate.

You can see here, cardiac arrest is the only cause of death in about 12,000 deaths a year. And, of course, everybody dies as a result of cardiac arrest. It just means that their heart stopped. So obviously, we need more information than that. But that's just to sort of illustrate the most extreme example. We also sometimes get drug overdose as the cause of death, and, of course, that's not particularly useful if you want to know what drug actually caused the death.

These sorts of problems, we know can be reduced through training and querying. We want to be able to get to the physicians, to educate them on the importance of the data. And in my experience in doing this -- I'm actually headed off to Nevada next week to

talk to physicians about this. And in my experience, once physicians understand the importance of the data that they're providing, they tend to take a little bit more trouble to provide good data.

As I mentioned, we provide training, sometimes in person. We also provide materials. And right now, we're working on an online tutorial that will help with this.

We also think that electronic death registration can help here as well. These systems can be configured to prompt the physician when they write drug overdose. The system could be configured to prompt the physician to specify which drug was involved and do it in real-time as they're filling out the certificate.

Now, with regard to drug-related deaths, there's sort of three general categories that we see in the mortality data. One involves sort of chronic abuse. This is sort of long-term use of a drug resulting in organ damage. These are usually certified as natural deaths, and so you would get this information from sort of a general physician. There

are adverse reactions in therapeutic use, and these are all coded in a separate section, and then the most common are the poisonings, the overdoses.

Some of the challenges that we have to deal with involve pending causes of death. And this is a particular problem with poisoning mortality, with overdoses or drug-related deaths in general, because toxicology tends to take a long time. In some cases, it can take weeks or even months to complete. And as a result, even if the fact of death is reported in a very timely fashion -- we may get the fact of death maybe in five days -- the cause of death may take much longer. And so what typically happens is the death certificate is filed and registered with the cause of death pending investigation, and then the cause of death is later amended to the certificate once the true cause of death is known. So that cause of death may come several months after the actual certificate is initially registered.

We also tend to have a problem in some cases with the timely filing of amendments by the medical examiners and coroners, and then once the state gets

that information, then transmitting that information to us in a timely fashion. We had a problem with West Virginia, I think it was 2005. When we compared our statistics for West Virginia against their statistics, we found that we had grossly underestimated their rate of overdose mortality. And this was because they had a retirement in their system, in their offices. And it just so happened that this person was responsible for sending us the amended records. And as a result, we got none of them. So all of these deaths were still pending cause of death, and as a result, when we closed our file, those end up as unknown, so we just code them to unknown cause of death.

Another problem that we have is with the coding system, The International Classification of Diseases, we're using the 10th revision right now. It's not very specific with regard to drug mortality. We have a code for opioid mortality, but it's a code for heroin, a specific code for heroin. There's no specific code, say, for oxycodone or hydrocodone or fentanyl, for example. We have a code for other opioids, and we have a code for sort of the -- I'm

blanking on the word right now. But at any rate, it's not specific enough. That's the point I'm trying to make.

That said, we do capture all of the text that's written on the death certificate, and so we can go to that information to find deaths related to oxycodone and hydrocodone and fentanyl and what have you. So we can get at that information.

Another thing that we're working on right now is suppose we are able to get this information in a timely fashion, and we hope that we will be able to, what are we going to do with it? So we've had to sort of reengineer our internal systems in order to be able to handle these data on a timely fashion and make sense of it in a timely fashion. And we are a statistical organization. We've been oriented for decades to collect all of the information and then process it, and the report it once we have it all.

Now we're sort of moving more towards a surveillance model, and we've got to figure out how we're going to deal with the data as they come in, look at it as it comes in and try to make sense of it.

And so we need to be able to code the cause of death in a much more timely fashion. We need to be able to edit it as it comes in, and then be able to perform queries, not just to the physician but back to the state if there are issues with the quality of the data.

So this gets to sort of the two questions that we're sort of grappling with right now, is once we have the data, what are we going to do with it? How are we going to make sense of it? Our goal at this point is to try to develop a capability of publishing quarterly statistics. So the idea would be in 2011, say, to be able to publish data for the first quarter of 2011 by, say, I don't' know, June of that year and to be able to analyze and look at the data from a surveillance standpoint during that period.

The other issue that we're grappling with is how do we disseminate these data. We have confidentiality restrictions, and as I mentioned, we're also sort of trying to wrap our heads around how we deal with data from a surveillance standpoint. We've never really done this before, and so it's going

to require some changes in policy and that sort of thing. And so we're going to have to figure out what data we can make available, and in what format, and who are we going to give it to and that sort of thing. And these are the sorts of things that we're going to be working on over the next year.

If you have any questions, you can feel free to contact me, either today or my e-mail and phone number are right there.

DR. KIRSCH: Thank you.

We're a little bit of ahead of schedule, so I'm going to take the opportunity to allow some of the committee members to ask questions that were cut off previously. So we'll go back to a question that was asked by Dr. Deshpande as one of the afternoon speakers has an answer.

Jay, did you -- Dr. Paulozzi?

DR. PAULOZZI: I think this was the question about race and socioeconomic status in relation to overdose risk, which came up this morning, and I haven't had a chance to share it with the questioner. But the short answer is there is a relationship with

race and socioeconomic status. Drug overdose rates in general are slightly higher in whites than in blacks. The rates are low among Asians and Hispanics. In general, people of lower income levels, such as people enrolled in Medicaid, have a higher rate of prescription drug overdose deaths. In the study in West Virginia, when we looked at pharmaceutical overdoses, higher risk was associated with lower educational attainment and the average income of the county of residence.

So in general, people with lower income and educational levels had a greater risk of drug overdose, and this correlates with greater rates of prescribing of controlled substances to people in Medicaid, for example, as opposed to non-Medicaid.

DR. KIRSCH: Thank you.

Dr. Terman.

DR. TERMAN: Yes, my question was for Dr. Conway. I don't know if he's here anymore. I was trying to get my --

DR. KIRSCH: No, he's not.

DR. TERMAN: I'll pass then.

DR. KIRSCH: Dr. Tortella.

DR. TORTELLA: Thanks. Two questions for Dr. Rappaport.

The first one, on your slide number. 2, it's a pity that the communication plan for REMS was not included, but I understand the constraints of the law and the generics and the FDA. My question would be, in those cases where there are generics in the market and a communication plan, what solutions would the FDA have to perhaps put a communication plan into play within these constraints and the obvious realization for the need?

MS. AXELRAD: Yes, if that's okay, I'll answer that. Basically, what we've found is that we can include the kinds of things that we would require under a communication plan, educational elements under elements to assure safe use. And as I indicated, generics, if there are elements to assure safe use for an innovator, then they would be required of the generic. So basically, instead of calling it an independent communication plan, we would incorporate whatever educational pieces we needed there.

DR. TORTELLA: That's good.

Then the second question for my colleagues there, on slide number. 3 and slide number 10, you talk about the goals and then the assessment. And I think it's careful to keep the two things at least separate in my mind, the first issue, have a REMS initiative, which seeks to reduce abuse, and then you have the REMS programs, which seek education and monitoring.

I'm just concerned that if a program is, in fact, accepted and executed and shows progress with education and with monitoring, but, sadly, the abuse continues, would that be construed as a failed plan and misbranded product? I don't think that's the answer, but I just want to get the clarity on it.

DR. RAPPAPORT: Okay. No.

DR. TORTELLA: Okay. Good. Thank you.

DR. RAPPAPORT: No. I think any inroads we can make in educating prescribers, we may not pick up the changes in abuse. We may not pick up changes in misuse at the same time, and I think we're going to have to be really cautious about interpreting any of

these metrics at this point. And it may take quite some time before we really get a handle on what it all means.

DR. TORTELLA: Okay. Thank you.

DR. THROCKMORTON: Bob, I think that's also a question that we asked for the committee to help us tomorrow as what we should think about when we get those metrics back.

DR. KIRSCH: Dr. Ballantyne.

DR. BALLANTYNE: I have a question for Dr. Rappaport, and it's concerning his first presentation.

I would like to know why the FDA has always been categorical about the extended-release or long-acting opioids not being used intermittently and what the basis for that decision was, whether it was based on evidence or just historical precedent, and what the concerns are in terms of whether it's a safety issue or efficacy issue.

DR. RAPPAPORT: It's primarily a safety issue. Our concern was that these are extremely potent, often high-dose products that really don't

necessarily need to be used when there are immediate-release products, which generally have less of a risk associated with them in terms of severe outcomes. So if you can use the immediate-release products, our thinking was that it would be better to do so when you can. And there are situations, we recognize, when it may be appropriate for a few weeks or something because there are advantages to the extended-release products. But in general, we felt that the risks outweighed the benefits of using them for settings where the immediate release could be used.

DR. KIRSCH: Dr. Denisco.

DR. DENISCO: Thank you. My question is either for Mr. Reuter or Dr. Rappaport.

A number of the speakers this morning mentioned a prior history of drug abuse as a possible determinant of oncoming history of problem. My training was to put the drug abuse in this situation, history in one of three categories, one, if the patient is in acute drug abuse and that led to their accident and that's why they're in the hospital; the second is they had a history of drug abuse or alcohol

abuse and it's been less than five years but they're doing well; and then the third is they have a very remote history of drug abuse, and it's been many years ago and they've done fine and actually had opioids on occasion with no trouble.

I was wondering how you were going to deal with that history in this whole schema that's being developed.

DR. RAPPAPORT: We're going to turn back to experts such as yourself and Nick Reuter and others around this table to put together the appropriate training for prescribers. We're going to have oversight to make sure that it's put together properly and that it's of high quality and that it's not biased. But we're not going to -- we really don't have the expertise to be writing this ourselves.

So does that answer your question?

DR. DENISCO: Yes. I perhaps jumped ahead.

The second question, to the same individuals or whoever wants to handle it, is the use of rescue medication for a patient that's on a long-acting medication but is still being prescribed intermittent

doses of short-acting medication, especially in cancer pain, which we're not talking about but this is commonly found.

Is this going to cause a problem with the review and analysis and everything relative to that?

DR. RAPPAPORT: I'm not sure I understand your question.

DR. KIRSCH: In deference to the next speaker, we'll hold the question for later.

DR. DENISCO: That's fine.

DR. KIRSCH: We'll now return to the program and ask Dr. Weiss to come and give her presentation.

DR. WEISS: Good afternoon. My name is Karen Weiss, and I'm with the Center for Drug Evaluation and Research at the FDA. And I'm here to talk briefly about the Safe Use Initiative, and in particular, opportunities to complement the REMS programs.

First of all, a brief introduction into the Safe Use Initiative since many of you may not be familiar with the program. Safe Use is an initiative at the Center for Drugs that was launched just the end

of 2009, and it's an initiative to reduce preventable harm from FDA-regulated prescription and over-the-counter medications. The goal is to promote drug safety outside of REMS, labeling activities and other regulatory authorities, meaning this is a voluntary initiative, voluntarily working with the greater part of healthcare community to develop interventions to reduce preventable harm.

We launched this because we know that FDA's regulatory authority, while very important, is not sufficient to minimize or reduce preventable harm. And the idea is to develop partnerships with healthcare, with government agencies, nongovernment organizations, any and all types of parties to come together to identify barriers to safe use of certain medications and to consider what kinds of interventions might be able to be developed and implemented to influence behaviors and practices.

We've launched this because we believe that collaboration can more broadly address the preventable harm from our prescription and over-the-counter medications such as misuse and abuse of opioid

medications, which is the subject of today's meeting.

So just to compare and contrast some of the activities, on the regulatory side compared to the safe use side, regulatory activities could include things like development and requirement for a REMS program, the subject of today's meeting, with all important aspects such as how to measure the impact; to require labeling changes, which you heard about earlier today from Dr. Rappaport that was done for certain classes of medications; to convene an advisory committee such as today; to require new studies to assess safety signals; to develop certain types of safety communications and put those out there; to develop guidance documents. Those are just some examples.

On the safe use side, we could convene stakeholders, bring together people on a voluntary manner, to work together to identify drug safety issues; to discuss barriers to their safe use; to consider what kinds of interventions might already be out there or might be able to be developed. We can form more formal types of partnerships with our

federal and nonfederal partners to work together to implement interventions and, importantly, to measure the impact. We could also join in ongoing drug safety activities. We can support broader types of safety types of activities such as health literacy and health information technology and many others.

In terms of how we want to prioritize activities for safe use, we want to consider medications that are associated with preventable harm that have a public health impact that are amendable to a collaborative approach to harm reduction, that are measurable and can complement ongoing regulatory activities if such activities are developed. And as you can see, the opioid issues really fit many of these types of criteria.

So I want to talk about a couple potential opioid Safe Use Initiative activities. The goals of these activities would be to, one, reinforce the REMS programs but also to expand into the areas where REMS is not appropriate, where FDA doesn't really have the authority to reach into those types of activities. And the opportunities that I'm going to talk about are

two, an education campaign and the patient/provider agreements. but there are potential for many more types of activities. And I really want this to just really be an open invitation to all of you to think as I go through this about are there potential opportunities, and we definitely want to hear from the larger community about where the FDA's Safe Use Initiative can work together to develop strategies.

So with respect to an education campaign, there would be -- and you've heard a little bit about some of the prior activities from Ellen Frank, and this would really pick up and expand upon what she presented. A campaign would involve a main message, and the message would be something like that opioids are powerful drugs and must be used only as directed. That's not exactly the exact wording. That would be yet to be developed.

It would ensure that target audiences understand the potential for misuse and abuse, and the target audience would be twofold. It would include consumers, patients, caregivers, other intermediaries, parents, healthcare providers such as the physicians,

pharmacists and others in the healthcare community.

It would involve communication of safe prescribing, dispensing, storage and disposal. And the campaign would be broader than what we're talking about with the REMS. It would educate about all opioid classes, not only the extended-release long-acting classes. And we believe the issues and the types of messages would be relevant regardless of the type of opioid.

Important parts of the campaign would include, of course, partnership developed with public and private partners to help in development of the campaign materials and messaging and to also to extend the reach of the campaign. There would be a variety of diverse channels, including a kick-off event and satellite media tour, considering a speakers bureau and using all forms of online and social media. And then the material disseminations would involve print and broadcast public service announcements and development and dissemination of collateral materials such as brochures.

Then I just want to move briefly to the

topic of patient/provider agreements or PPAs, and these go by many different types of terminologies. But in general, they're written documents that are oftentimes signed by both patients and providers that describe patient responsibilities such as the fact that they are to take the medication as prescribed, that they're supposed to attend required follow-up visits, that the patient is to inform the doctor promptly of side effects, that they're to use one doctor and one pharmacy, and that they will not sell, lend or otherwise give their medication to anybody else. And it also provides information on such things as proper use, storage and the risks. A few of these contain provider responsibilities.

PPAs have both their positives and negatives. They provide a tool for discussion. They can increase awareness about these medications. They can serve as a reference tool for home use. They can be used as a springboard for developing a broader health plan and reevaluative type of proposals, and they do clarify patient roles and provider roles and responsibilities. But on the downside, they may

not be geared at the appropriate literacy level. In fact, there is a recent review from 2007 looking at about over 100 and some, close to 200, of these types of agreements from individuals who were members of the American Pain Society, and they found that the majority were written at the 13th or 14th grade level, so pretty high level for maybe the average patient.

They may have an adverse and negative impact on the patient/provider relationship. They may have an emphasis more on patient compliance. As mentioned, they often lack provider responsibilities. They may have inadequate highlighting of benefits and risks. In fact, they may actually tend to defer individuals who maybe need these medications from actually taking them. There is sometimes stigma associated with them. The documents themselves can be very long in addition to not at the appropriate literacy level, and there are limited data on their effectiveness.

So we can see a number of potential opportunities for Safe Use Initiative in the arena of patient/provider agreements. There's a number of areas of research, including who uses an opioid PPA

and why, how well do they work, what do you actually measure. You'd obviously like to see that it has some benefit in terms of health outcomes for the patient; what kinds of information should be in there; what is the type and format of the information; what are the essential elements, the layout, the consistency; and what's the proper balance between provider and patient responsibilities. And then if there is some type of agreement through a partnership, that we actually think that these are good things to more broadly have out there in the community, then how do you ensure and encourage that they're used.

So just in summary, I've highlighted two potential opioid Safe Use Initiative activities, an educational campaign, patient/provider agreement type of activities. There are many issues to consider in both of these, including are these appropriate activities for Safe Use Initiative. If so, what are the best ways to measure their impact? As we've discussed, measurements are very difficult when we're talking about REMS programs, and they're no less challenging in some of these other types of

activities.

We anticipate developing other safe use programs to enhance opioid safety, and we are definitely interested in seeking input and partnership on various types of activities that you-all think would be relevant and appropriate for FDA either to join on to existing activities or to be involved in the development of new activities.

So just in final closing, we have a number of ways that we can actually hear from you, and we would definitely want to do that. There's a website for our Safe Use Initiative. We have an open docket for safe use, and we would be very interested and encourage anybody who wants to, to provide comments to the open document. And we also have a safe use e-mail account where we can actually receive information from you. So thank you very much.

DR. KIRSCH: Thank you.

We will now take a 15-minute break. We'll reconvene in this ballroom at 2:40. Panel members, please remember that there should be no discussion of the issues at hand during the break amongst yourselves

or other members of the audience. Thank you.

(A recess was taken.)

DR. KIRSCH: Our next speaker is Dr. Murray Kopelow from the ACCME.

Dr. Kopelow.

DR. KOPELOW: Thank you, Mr. Chairman, to the advisory council and to the guests.

My goal is to describe the accredited continuing medical education enterprise of the United States as a potential resource to FDA and to the strategies surrounding REMS. The Accreditation Council for Continuing Medical Education, of which I am the CEO, is an organization created in the mid '60s, then reconstituted in 1980 by these seven member organizations, the principal organizations of medicine of the United States.

The scope of our enterprise is considerable. We have about 2,200 accredited providers distributed across the United States, including Hawaii and Alaska, even though I neglected to leave them on the map that are on the graphic. There are more than 17 million participants in our accredited system annually, close

to 100,000 activities and over 700,000 hours of instruction. There are more than 300 accredited continuing medical education activities per day in the United States involving more than 40,000 physicians and prescribers.

Accredited continuing medical education has been and is a link to professional practice and focused on improving quality gaps. That's the same goal as the REMS. Our system uses practice-based needs. It matches the content of education to the scope of the physician's practices and it is involved in measuring change in competence or performance and patient outcomes as part of the CME process.

Our accredited system is evidence based. Both from an educational perspective, we use the evidence base of a proper education as well as that we have an evidence base of the effectiveness of continuing medical education in changing knowledge, competence or performance. These data are at the meta-analysis and meta-synthesis level as well as at the randomized control trial level.

Our system for some time has been focused on

improving practice gaps using national data. The data at the top are from the Rand Corporation, on the right published in the New England Journal on Pediatrics in 2007. Disparity data like the one in the bottom left-hand corner, the mortality rate of African American women from breast cancer in the Chicago area is 70 percent higher than for white women. And the CME system got together to focus on addressing that professional practice gap.

In the bottom right-hand corner is data from SAMHSA and the Office of National Drug Control Policy, the kind of thing that our CME system has been trying to use, the same kind of data that REMS is based on and what we've seen today as the potential metrics for the measurements.

But it's important to understand continuing medical education in a manner very differently than Dr. Gallagher described first thing this morning. Continuing medical education is not a lecture. It's not a seminar. Continuing medical education is based on questions in practice developed from practice, and people go out and seek new data and information that

they analyze and synthesize into new knowledge. The application of judgment and wisdom to that knowledge, new strategies are developed, new competence, new ability. You put that competence or ability into practice; that's performance.

This circle, which is a merging of the educational measurement language and the knowledge management language, this is what we refer to as the continuing professional development of physicians and professionals. This is what individual people do in order to answer questions in practice.

Continuing medical education is superimposed on CPD, on continuing professional development. Continuing medical education are a series of events or activities that help physicians move through the transition of continuing professional development.

Self-assessment is a refinement of questions in practice. Didactic and plenary sessions like the web, like the journals, like the books are getting data and information. Reflective small group study and interactive sessions like we heard earlier today that SAMHSA is involved in helps people develop new

strategies and new competence.

If hands-on is required like we deal with people in the device industry or psychomotor skills, that's the next step. And then to overcome system obstacles is the next step in continuing medical education to promote physician change and physician performance improvement.

So to go back, if REMS wants to promote change in what physicians do, the system needs to be respectful of this series of events. And this is what needs to be supported by industry and by the REMS strategies. In order to support the development, we need the creation of appropriate continuing medical education to drive physician change and improvement.

Now, I say physician because I work in the continuing medical education enterprise, but these are applied to professional education, the pharmacy to nursing to physician assistants. To everyone who is involved, these are the principles of changing professional practice.

Historically, we've been involved for a long time with addressing overuse, underuse and misuse in

clinical care. But it's very important that the interventions include those that are predisposing to change as well as enabling as well as reinforcing. People don't know they don't know. They know they don't know. They think they know and they don't, and they think they know and they're right. And it is important to move people across that continuum.

I had the honor of being a special advisor to the Office of National Drug Control Policy in the executive office of the president in the last half of last year. And what we learned when dealing with physicians, what I learned, is that the physician community doesn't know that 1 in 12 of us, all of us, 1 in 12 of us is abusing some sort of chemical. They don't know that these issues are to be addressed. It isn't at the level yet throughout the profession that they're not asking because they don't know what to do with the patient; they really think that they don't have any addicted or abusing patients in their practice.

Predisposing people to learn is a challenge for all of us. Enabling them to change is what

traditionally we think of continuing professional education, and then reinforcing those changes with reminders, with electronic medical records, with colleagues who know, with team-based care, with patients who understand what questions to ask, with our colleagues the pharmacists phoning us and talking to us about this prescription, these are all areas that the literature has shown since 1999 are important in continuing medical education.

On July 22nd, I got a letter of invitation from you to this meeting, and you described in two parts of this letter of invitation the needs data, the professional practice gaps that could empower and enable the CME system for the next two decades full of continuing education activities. And there is a system in place already to promote the kind of education that you want. We have educational requirements, and we have standards for commercial support that manage the boundaries between industry, between what you're referring to as the sponsors and our learners, the prescribers.

These have been validated and valued by the

system in which we operate. On the left-hand side, the former president of the Federation of State Medical Boards is talking about our educational requirements as we rolled them out, and just two weeks ago, the deputy director of NIH talking about the value of our requirements in managing the boundaries between industry and the medical profession. In this context, it was control of content in the hands of industry at the discovery stage, at the translation between discovery and first use, discovery and publication. And like Dr. Rappaport said, when we found that the control of the content of the education was truly in the hands of the specialty societies, our rules were removed as a barrier to the promulgation of the new information.

It was an interesting read of the prescriber education working group and the materials that you transmitted. And on the left-hand side are the words of that group talking about the goal of the CME should go beyond traditional knowledge acquisition and instead aim to demonstrate optimized practitioner performance and improved patient outcomes.

In the words of our updated criteria released in 2006, you'll find the same language. And this alignment of purpose speaks to the value of integrating REMS and the prescriber education in REMS into accredited continuing professional education. And we said in 2004, professional development based on continuous improvement in knowledge, strategy, performance and practice necessary to provide optimal patient care. Our goals are aligned.

We've translated that into the real words of our requirements, some of which are reproduced here, where the providers are required to incorporate the educational needs, either knowledge, competence, or performance, based on the professional practice gaps. So when we can show the CME provider system that which the physicians aren't doing completely, and what underlies that gap is what the CME system needs and which is completely aligned with you.

They must design educational activities to change competence, performance or patient outcomes. And we use competence analogous the same as strategy; not is it good enough to deliver care but do they have

the strategy, and if given the opportunity, they would put it into practice.

We require our providers to use the appropriate format to what it is they're trying to accomplish. If you're trying to change knowledge, then give a lecture because that's what you're trying to do. If you're trying to change strategy, teach and evaluate with standardized patients because those are designed to change people and measure people's strategies to deliver care.

We require our providers to analyze the change that they cause through their educational interventions. So to me, a gift was the list of metrics that I saw from Dr. Weiss, the list of metrics that we saw all day long. Those are parameters and variables that we can use to design the educational interventions and measure the success of the educational interventions.

We go beyond that because it isn't just a change in physician knowledge that will change the health outcomes that you're talking about. It is the extent to which the accredited providers interact and

engage with the environment that they are in, the extent to which they involve themselves in efforts to improve professional practice, that they use these noneducational strategies, that they identify the factors outside their control that are impeding the progress or change in practice, that their job is to overcome and remove barriers using educational methods where possible, to collaborate and build bridges with other organizations and participate within a system framework for quality improvement.

The accredited provider is a change agent, not just an educator or a teacher. And this isn't new. This is the model. This is the message we've been flogging through accredited continuing medical education for the last number of years, that our accreditation expectations linking through practice have the goal of change and improvement.

REMS and opioids isn't the only one, and there's a long line of institutions and organizations who want their education to be the top of the list. But there are a lot of accredited providers that will support and be interested in the REMS movement.

I agree with Dr. Rappaport that our standards of commercial support should not be a barrier to this. Now, we created a set of standards of commercial support to ensure the independence of accredited continuing medical education from the influence of the pharmaceutical and device manufacturers at the request, quotation marks, of the Food and Drug Administration two decades ago, led by Senator Ted Kennedy's hearings on Senate, followed by actions of the American Medical Association and the Food and Drug Administration.

We've been struggling to ensure independence for years. Things are changing, and in the context of REMS, there's three players, maybe four. But there is the Food and Drug Administration and control of content, industry tasked with the charge of ensuring that there is education and then the whoever it is that's going to deliver the education. The control of content can stay in the hands of the Food and Drug Administration. And if the sponsors can become responsible for ensuring that education occurs, I believe that the accredited continuing professional

education enterprise can design and create the education.

It can be inside the government or outside the government. We accredit the FDA, the CDC, Uniform Services Hospital, the Army, the Navy, a dozen elements of the federal government. The Food and Drug Administration could drag the accredited provider in to partner with the communications staff who are developing a lot of the education, but also there's another 2200 accredited providers who are trying to do this, to ensure that this downstream effect of the presence of industry is not more use of something than is necessary. And we've got a series of internal controls that are in place to prevent that, that we say explicitly that guidance cannot come from industry about what should be in the content of continuing medical education. It must be created independently. It must be based on professional practice gaps. It must be content valid. And what we're saying is that the FDA needs to help us with these four or five top priority areas as we develop the accredited continuing medical education with a special role for industry as

prescribed by you to ensure that propriety occurs.

I want to end with just some comments about the middle of that paragraph of the letter that you sent us on July 22nd. "Require a much broader set of interventions coming from the numerous stakeholders affected by this crisis."

We can change what physicians know. We can contribute to a change in their strategies, what they would do if they were given the opportunity. But the system affects what it is that they do in practice. There's no single silver bullet, no single intervention available that will change practice. And what she does as a professional is determined by the environment in which she operates. Administrative issues, group norms, professional regulations, environmental factors all contribute.

So if you're looking at a continuum of change with at one end regulation and coercion, at the other end the facilitating conditions of education, there's an important middle section which has to do with affecting the practice environment and the way the physicians practice medicine. There's four

variables that really affect it from the social science literature, habit and intention, motivation and facilitating conditions.

Habit and intention both have to be zero to make change zero. Motivation and facilitating conditions are the much more important factors. Accredited continuing medical education lies in the facilitating conditions section of this. There are other factors that you've talked about today and have been in your literature about motivation, but changing intention and changing habit is an important part of what Dr. Gallagher talked about this morning. We've got to get to the students and the residents for this to become the way that they practice their medicine.

The ACCME and continuing medical education believes that accredited continuing medical education has a place in addressing the national priorities and the national gaps. We would welcome the opportunity, the challenge, that this would present to us. In the context of our weaknesses and our limitations, we see this as an incredible opportunity, and we do have some of the strengths that could deliver it.

If you look in the National Drug Control Policy that was released earlier this year, the President did include accredited continuing medical education and professional education in several elements of change and improvement, which we would welcome the REMS as part of that larger strategy. Thank you.

DR. KIRSCH: Thank you.

Our next speaker is Dr. Peter Vlasses.

DR. VLASSES: Good afternoon, and thank you for the opportunity to speak with this afternoon about REMS and continuing pharmacy education.

First, I'd like to say that ACPE, the Accreditation Council for Pharmacy Education, has many similarities to ACCME. We believe in the same principles and have cooperated with ACCME in a number of initiatives. So I will try and build upon what Dr. Kopelow has said and focus more on pharmacy education accreditation issues relevant to REMS issues. As you can see from this slide, pharmacists educating health professionals or specialty pharmacies or assessment of REMS performance

all may interact with the pharmacists or pharmacies. And as I heard today, the Safe Use Initiative has some educational issues, and again, some of my comments may be relative to that as well.

So I'd like to first introduce you to our organization, talk a little bit about continuing pharmacy education, talk about some data that we have collected and the potential to collect more, and then how does this all interface with REMS, and then be able to answer any of your questions.

We're the national agency for accreditation of pharmacy education. We accredit both the degree program in colleges and schools of pharmacy in the United States, and we're recognized by the U.S. Department of Education and the Council on Higher Education Accreditation. And we also accredit the providers of continuing pharmacy education.

We were founded in 1932 by the same three organizations that continue to support us and appoint our board; that is, the National Association of Boards of Pharmacy, the American Association of Colleges of Pharmacy, and the American Pharmacists Association.

We were asked in 1975 to add accreditation of CE providers to our mission as mandatory continuing education became more involved in pharmacist relicensure. We're an autonomous, independent, not-for-profit agency headquartered in Chicago.

ACPE is one of 11 organizations that is part of the Joint Commission of Pharmacy Practitioners, and this group published a vision several years ago that said that pharmacy education and continuing education would prepare pharmacists to, first of all, provide patient-centered and population-based care that optimizes medication therapy; manage healthcare systems' resources to improve therapeutic outcomes, including the dispensing of the drug product; and promote health improvement, wellness and disease prevention. I think you can see that all three aspects of this vision relate readily to the purpose of the REMS program, and this vision forms the basis of our standards for both degree programs and continuing education providers.

There's about 265,000 licensed pharmacists in the U.S. All states and territory pharmacy boards

require continuing pharmacy education for pharmacist relicensure. There's an average of 15 hours per year required, but it ranges. We have close to 400 ACPE-accredited CPE providers, and activities done by these providers or put on by these providers are accepted for mandatory licensure requirements by all state boards of pharmacy and for licensed transfer and for people having multiple licenses.

Our providers are divided across these groups, colleges and schools of pharmacy, education companies, hospitals and healthcare networks, associations and publishers, government agencies and others.

These slides are real hard to see, but this is on our website, and this is called the provider web tool. This is a tool where the providers of continuing education supply data to us on application or knowledge of continuing education activities, or practice activities, which I'll define, and give us, currently on an annual basis, how many pharmacists participate in which specific programs or which activities.

So the way we do this is we have a universal activity number. Each provider has an ID number. The release date is specified in terms of the year. There's a sequence about which number of activity it was per given year, but more importantly, there's some topic designators in terms of what the continuing education was about, including one on patient safety. It tells us whether this was a live activity, a home study or combined. And it tells us whether the audience was pharmacist or technician.

From that, we can develop data such as this. This is for the year 2008-2009. We had 396 providers, and you can see here there were 25,000 plus activities that were participated in by over 3 million pharmacists. The participant numbers then would include the same person more than once. If somebody is getting 15 hours of CE, this will be the number of pharmacists multiplied times the number of hours that they participated in. Pharmacy technicians are a growing group, and they also are embedded in the database.

We've seen changes in how activities are

being provided. Here we had in 2001-2002 and 2008-2009 about the same number of providers, many more activities in the last time we looked at this. You can see that if you looked at live versus home study activities, a changing pattern with home study activities now being the predominant way that pharmacists and technicians are getting their continuing education primarily driven, we believe, by economic issues and time away from work and a number of other variables.

So for the opioid REMS relevant activities, we have key words that we could search, and we found that about 3 percent of the activities in the last year and about 5 percent of the number of participants were involved in REMS-related activities. And when we looked at specific keywords, we could go down and look at a particular activity and the number of participants.

We have recently modified the types of continuing education activity to be one that's primarily the transmission of knowledge, another that requires the application of information in case

studies and the application of principles through active learning strategies, and what used to be called certificate programs, which are now practice-based activities that involve installation of knowledge, skills, attitudes and behavior with demonstration of performance.

The exciting thing we're involved with currently is a project with the National Association of Boards of Pharmacy where we hope to take this database from the capture of aggregate pharmacist data on an annual basis to the capture of individual pharmacist's activities by title, format, date, et cetera, on a monthly basis. And this is all stored in a secured electronic database of pharmacists profiles that is being built at the National Association of Boards of Pharmacy.

We have targeted July 1, 2011 for completion of this database and that we believe such a database could develop REMS-specific tracking systems or other things relevant to REMS whether it be opioid or other types of REMS.

Along with what Dr. Kopelow said, the

achievement and impact of the CPE mission and goals, we are looking at measurement of issues not only of participation and satisfaction in the educational activity, but rather what learning took place, what performance has changed, and more and more, looking at specifically patient health and population health data that can be developed as part of the educational program activity.

Again, we have formally adopted the ACCME standards for commercial support, so everything that Dr. Kopelow has said would also then be relevant to continuing pharmacy education in meeting these standards and making sure that exactly the way he described it would be appropriate for ACPE.

So as with the CME providers that Dr. Kopelow mentioned, I think that the 400 CPE providers, if asked, could produce specific CPE to support product use of drugs under REMS. The evaluation and measurement and effectiveness of REMS educational activities could be fostered through either the providers or through our central database, and to facilitate change in data, including individual

pharmacist CPE documentation, which has been thought to be problematic to this point. But again, one could search by topic, perhaps a new topic designator for REMS or a particular REMS activity, and then be able to search which pharmacist took which program or activities and create a database that would be relevant to trying to improve the patient care. Thank you.

DR. KIRSCH: Thank you.

We now have some time for some questions.

Dr. Turk.

DR. TURK: Thank you. This goes back to our morning presentation, but also it seems to have been picked up this afternoon. And it was really two questions, one which really may have been appropriate for Ms. Frank but could be for anybody else as well, which is it sounds like the FDA has done -- and maybe SAMHSA as well, have done a nice job of developing lots of materials for education and for communication. But it feels a bit as if it's something of a shotgun rather than a rifle.

We're throwing lots of things out there, and

I'm wondering about how the evaluation processes are performed to identify which of these strategies, materials, approaches, actually to the types of change that are important and that should be continued versus left along the way.

So that's question 1. Do you want to, I guess, address that first?

DR. KIRSCH: Yes. Will someone from FDA take the question?

DR. WEISS: Unfortunately, I know Ellen Frank had to attend some other conflict this afternoon, and she's the one who's really the expert in the whole arena of the public education and outreach.

I do know -- and if she has any colleagues that are here that want to speak; somebody may also be here from her group. One of the, I think, difficulties has been pretty much what you've said, that it's been put out there. But there really hasn't been any formal measures or test to assess the reach of the programs, because there are different ways to measure success, if you will, and that includes is the

information getting to its intended audiences. Another thing is, is it affecting some kind of change, things that Dr. Kopelow was talking about.

I think that certainly as we're thinking about safe use in a broader type of educational campaign, there would be some really need to develop methods, both before and after or during, et cetera, to really assess what is being delivered and its effectiveness and how to modify or change, should that be done. I think that's a very important question, and I think it's very complex. And that's sort of my thoughts about that arena.

DR. TURK: Can I follow that up? If a large number of different efforts are taken at the same time, it's very difficult to know which is having the effects and which are not having the effects. So if we're thinking to develop programs for REMS, what can we learn from those previous efforts that might help us? And just a crude example, if we started something as a physician education and a patient education at the same time, how would we be able to determine how those fit together?

DR. WEISS: I think there's others that are probably better to -- we've come up with that very same question not only with -- we're talking about opioids, but other types of safety issues. Because oftentimes things do occur in either sequential or pretty much at the same time, and I think a real challenge is to tease apart what is the contribution. One might say, well, the end result is that you want to improve safety or patient outcomes, so maybe it doesn't matter. But it clearly does matter because you want to know what's really working so that you can apply it or modify things that aren't working. So Bob and maybe some others from the table might also have some thoughts in that arena.

DR. THROCKMORTON: I guess I just agree that this is a terribly important topic, and we are asking for your help on this question as well tomorrow. I think it's, in fact, the last question of the day is how do you distinguish these different efforts.

One thing just to bear in mind, though, is, of course, just because it is challenging to distinguish the impact of the one area versus another

doesn't mean that you might not undertake all of those various things together even if they are challenging to decide one is working and the other one might not be.

DR. TURK: My second question, which relates to this, is when we're thinking about long-acting opioids and we're thinking of people in chronic pain, we're thinking that these are people who potentially are taking these for long periods of time. I've worked in pain clinics, and the mean duration of pain the patients come in there is seven years. So I'm wondering -- and I heard this from Dr. Kopelow which was very good -- is that one-hour training or one time going over with a tear sheet may be fine to initiate some change. But what is being thought of as far as maintaining the change for people who may be taking these medications for years, if not decades? And I'm not sure who to address it to.

DR. RAPPAPORT: Well, if you're addressing that to the agency, that's exactly, again, the reason that we've brought you all together here, is those are the questions that we need you to answer as well as

not necessarily today, but to take on the responsibility of figuring out how to properly educate prescribers and patients and codify that, and then to figure out how to evaluate and assess how well we did it.

DR. KIRSCH: Dr. Berger.

DR. BERGER: Yes, this is a question for Dr. Paulozzi.

On your suggested metrics, on your provider education -- is Dr. Paulozzi still here? Gone?

DR. KIRSCH: He's gone.

DR. BERGER: Okay. There were some suggested provider education on suggested metrics on dose escalation of methadone, which would probably not apply for palliative care patients at all, like at all, of 50 percent increase in dosage each month. It wouldn't apply at all. So just a note.

DR. KIRSCH: Thank you.

Dr. Flick.

DR. FLICK: This is for Dr. Rappaport.

In your presentation, you talked about one of the elements being prescriber training, and the

prescriber training would require that the sponsor would be required to demonstrate the prescribers have been trained and that knowledge of appropriate use has improved via surveys.

Who would create those surveys and would they be approved by the agency and who would administer them? Because clearly, these surveys are potentially biased and the sponsors have an interest in ensuring that this education has occurred.

DR. RAPPAPORT. Yes, once again, we'd have oversight over the actual -- although the sponsor would create it, we would have approval rights over it, and we would then see the data and evaluate it ourselves as we do with all data that's submitted to us.

DR. FLICK: That raises the second question, which is, I think, in the past the agency has had trouble with, for example, marketing that has been required to be approved by the agency, sponsor marketing, but there's a backlog. And your ability to review all this material is limited.

Will you be able to review all the material

that comes in?

DR. RAPPAPORT: Well, we're certainly going to try.

[Laughter.]

DR. RAPPAPORT: With marketing materials, it's a very different issue, and then up until recently, we didn't have a lot of authority in there, and even now, we have less authority in terms of marketing than we do with REMS in terms of going over these materials. We will do our best to review these, and they won't be approved for use until we do review them. So obviously, the onus is going to be on us to do it in a timely manner.

DR. KIRSCH: Ms. Krivacic.

MS. KRIVACIC: Yes, thank you. I have a couple questions from mostly this morning's session for Dr. McLellan.

Is he still here?

DR. DORMITZER: He's gone.

MS. KRIVACIC: Okay.

Then, Dr. Dormitzer, regarding your slide showing the patients that received prescriptions from

their friends, which were then received from a doctor, do you have any information on who those actual prescribers were, what specialty they were, the doctors that the friends received --

DR. DORMITZER: (Off mic.)

DR. KIRSCH: Please go to the microphone.

DR. DORMITZER: The National Survey on Drug Use and Health does not collect information on what type of physician, just where did they receive the pain reliever from.

MS. KRIVACIC: Okay, so not the specialist.

DR. DORMITZER: No.

MS. KRIVACIC: Okay. Thank you.

Then I did have one other question for Mr. Paulozzi, but I guess he's not here either. But I did notice that the PMPD program for the state of Washington is currently not active. And I understand from one of our past meetings here that Washington state did have a pretty high ratio of overdoses for the young, I guess the adolescents and teenagers and college students, with regard to OxyContin.

I'm just wondering -- I know it's for

budgetary purposes, but if we're going to look at PMPD databases, I wonder if we're going to run into this problem with other states because of the economic situation. Just a comment.

DR. KIRSCH: Thank you.

Dr. Morrato.

DR. MORRATO: This was a question that also goes back to this morning, and Dr. Rappaport was talking about the history of the labeling changes over the last decade. And I know you mentioned that there was a risk management plan that was put into place in, I think, 2002 or so. And you talked about as part of that plan there was an education component, which included accredited continuing education.

I was wondering if maybe you could share some learning from that as to maybe a bit to describe what was its scope and scale in terms of if we have any information on how it was actually delivered, the messages or behavior change and was there any evaluation specific to those education elements that was done.

DR. RAPPAPORT: Could you repeat the

beginning of your question, please?

DR. MORRATO: So earlier this morning, I think you talked about the history. It was slide 14 when you were talking about the addition of boxed warnings and how it went from potential abuse and all of that language. And then there was a slide that talked about the risk management plan, and there's an element in there that says education. And part of that was accredited physician, nursing, pharmacist continuing education programs that were performed. And I didn't know if we had any information on what their design was, implementation or any learning on their effectiveness.

DR. RAPPAPORT: I don't have any information on that here, and I doubt that anybody here does. We could try to find it for you. What I can tell you is we probably don't have an adequate way to measure whether it had any realistic impact.

DR. MORRATO: Right, so okay. We're talking about education again, and so as we heard in terms of the accreditation board, that's a very broad term. And we want to be careful that we don't lump

everything in the same bucket just because they say they're doing continuing education. We kind of need to differentiate in terms of the scale and so forth. So I guess historically, there was no evaluations done.

DR. RAPPAPORT: That's correct.

DR. KIRSCH: Thank you.

We'll now go back to the agenda and start the industry presentations. Our first presenter is Mr. Lessem.

MR. LESSEM: Good afternoon, and thank you to the Chairman and the members of the advisory committee for being here today. My name is Martin Lessem. I want to once again just begin by also thanking the FDA for the opportunity to address you today on behalf of the industry working group.

I will be providing a brief introduction and then handing the presentation off to my colleagues, Dr. Eric Davis who will discuss the REMS components, and Dr. Paul Coplan who will discuss the REMS assessments. It's important to note, however, that we're today representing the industry working group

and we're not here representing our individual companies.

The issue before this committee today is one which has interested parties from all over the spectrum. In our case, the industry working group or IWG was tasked back in March of 2009 by the FDA at a meeting in Silver Spring to work together collectively to develop a risk evaluation and mitigation strategy, or REMS, for the extended-release and long-acting opioid products of oxycodone, morphine, oxymorphone, hydromorphone, transdermal fentanyl and methadone.

Throughout our presentations, the members of the IWG will use the term "long-acting opioids" to refer to all the products under discussion today, those that are inherently or pharmacologically longer acting than most other opioid analgesic drug substances and those that are made long acting by being formulated in extended-release oral or transdermal delivery systems.

We requested to speak today to show our support to the FDA's REMS but also to suggest additions, which through our work in developing REMS

and working with stakeholders, we feel would complete the FDA's REMS and create a long-term and vital final product.

In addition to the presenters, we have some of our colleagues from the IWG with us to assist in answering any questions which may come up. These are drawn from our various sub-teams and have expertise within their specific areas.

Many of the concepts which both our subject matter experts and us three presenters will be speaking to were developed through many face-to-face meetings, including two public meetings with the FDA and various meetings with stakeholders to vet our ideas and gain a better understanding of what the medical, dispensing and patient communities view as an optimal direction for the opioid REMS.

The 20 individual sponsor companies, which are listed on this slide with products that are currently subject to the REMS for certain opioid drugs, have worked collaboratively as requested by the FDA. The IWG REMS and supporting documents, which the FDA tasked us with back in March of 2009, was

submitted to the FDA on July 8th, 2010 and has, to the best of our knowledge, been shared with this advisory committee.

The IWG supports the approach proposed by the FDA and will work diligently with the agency to refine, finalize and implement the FDA's proposed REMS. We would like to offer some additional considerations where other options may offer some additional value.

As a general overview, I would like to take a very brief look at the sections of both the FDA and the IWG REMS. In the next few slides, I will highlight a few of these sections and give you some brief introductory thoughts on them.

Before I move on, I would like to draw your attention to the similarities shown here. The two main recommendations for additions are multiple medication guides, which I will briefly cover in a moment, and also, a communication plan.

Regarding the scope of use, the agency's goals include nonmedical use, whereas the goal proposed by the IWG is limited to the legitimate

medical use. As FDA has stated in their background material, a variety of behaviors are likely contributing to the adverse outcomes associated with the long-acting opioids. The IWG agrees with this. While the REMS may be able to influence those behaviors related to medical use through prescriber and patient education, FDA has acknowledged that both diversion as well as other illegal activities also contribute to abuse and misuse. Therefore, the goal as proposed by the IWG limits the scope to the legitimate medical use based on what sponsors can effectively influence.

Another area where differences arise is in the medication guides. At our December 4th public meeting with the FDA, it was made clear that the FDA would prefer a single medication guide, which the IWG then began working on. However, based on stakeholder input and feedback, the IWG has looked instead at three separate medication guides which give us not only the most flexibility but also the most directed coverage in regards to patient and caregivers and risk information.

The three medication guides, which you can see on the slide, are one for the general class of oral long-acting opioids, one for the long-acting opioids with a transdermal delivery system, and one for methadone tablets and oral solutions. The reason for these three separate medication guides is based on these discussions with stakeholders and will enable caregivers to better convey to patients the safety and risk information in a more effective manner.

One area where our proposal augments and would strengthen the FDA's proposed REMS is with the inclusion of a communication plan. What the IWG proposes is to directly communicate to healthcare providers and also through the various professional societies and licensing authorities the existence of the opioid REMS and also the risks inherent in prescribing these products. This communication folds in very closely to our prescriber training, which Dr. Davis will cover in our next slide, and was compiled by both the generic and the branded companies in the IWG.

When we come to the REMS assessment, there

is one major item for this committee to keep in mind, and that is that the sources used for data are critical to how one assesses the REMS. Dr. Coplan will go into this in considerable detail, not only in what it is hoped to be measured but in also how to go about it.

As with the rest of the REMS, the IWG is committed to continuing a working relationship with the FDA and other parties to ensure that the final assessment plan is both substantive and meaningful.

As was mentioned earlier, there are similarities between the FDA's and IWG's REMS. We feel that where the differences occur, which will be further explained in our subsequent presentations, the IWG's proposal can augment and help improve the FDA's REMS. It's important to point out that the spirit of the documents are the same and aim to responsibly and effectively manage the risk of these important medications while maintaining access to these medications for people with chronic pain.

I would like to thank you for your time this afternoon, and it is my hope that I have effectively

shown you how the IWG has been working diligently since the beginning of this process in parallel to the FDA. Before I turn the presentation over to Dr. Davis, I want to reiterate that the IWG supports the approach proposed by the FDA and will work diligently with the agency to refine, finalize and implement the FDA's proposed REMS.

It's now my pleasure to hand the floor over to my colleague, Dr. Eric Davis, to expand on the proposed components. Thank you.

DR. DAVIS: Thank you, Martin.

Mr. Chairman, members of the advisory committee, good afternoon. It's my pleasure to be here to discuss the components of the IWG REMS. IWG and FDA agree that prescriber and patient education will be very important and will be key components to an effective REMS. The question becomes how do we develop an effective program that does not create a burden on the healthcare system nor does it limit access to patients to these important medications.

For the most part, the REMS that was developed and proposed by IWG is quite similar to that

that was developed by FDA. This point is very reassuring. But over the next several moments, I'd like to expand on the results of our work and point out some of the components that might complement FDA's proposed REMS.

This education would be available in many different forms and would reach those involved with the prescribing, dispensing and use of long-acting opioids through different means, much the way FDA had talked about a multi-prong approach. The IWG proposes the use of multiple tools in disseminating this important information about the REMS. These tools would be in the form of medication guides, a communication plan and elements to assure safe use.

Medication guides are an important part of most REMS, and they can convey important safety information about the product. It was our charge from FDA to develop a single med guide for all of these products, and the IWG worked hard to achieve that goal. However, this single medication guide was quite long, and it really didn't lend itself to ease of use from the patient perspective.

Although all of these products have similarities when it comes to risk, there are enough nuances and differences in the risk profile that a concise patient-friendly version couldn't be written which contained all of the necessary safety information.

For example, medications for most of the oral forms have warnings about crushing or splitting tablets while the patches seem to be more concerned with the delivery and application uses. Another example would be that of methadone, which has specific cardiac warnings. Therefore, we took the next logical step, which was to propose a reduction in the number of medication guides from more than 20 to three.

These three medication guides, one for oral long-acting analgesic medications; one for the long-acting transdermal products, and a medication guide for methadone, hydrochloride tablets and solution; they all contain the same safety language, but they also provide the patient with information about the particular route of administration or the product's specific risk.

The next tool for consideration is a communications plan. The use of a communications plan could be utilized to inform healthcare professionals of the existence and the timing of REMS. These communications would also help to ensure the benefits of the long-acting opioid analgesics continue to outweigh the risk by reducing the potential for abuse, misuse, overdose and addiction from the legitimate medical use of these products.

As part of the communication plan, letters would be sent to the following audiences: prescribers who we know prescribe or are likely to prescribe long-acting opioids; pharmacies; state medical nursing and pharmacy licensing boards; targeted medical nursing, pharmacy and patient associations; and other DEA registrants not covered by the prescriber mailings. This might include individuals who have Schedule II prescriber authority but have not recently prescribed long-acting opioids. These letters would not only contain important information concerning the REMS but would also contain information about where additional REMS information can be found.

Starting with the prescribers, the following package of materials would be mailed to prescribers who routinely or have recently prescribed long-acting opioids, say, within the last six months: There's be a dear prescriber letter; medication guide; a patient medication information sheet, which will be described in a moment; training guides for prescribers as well as training confirmation forms.

The patient medication information sheet or PMIS is best described as where patient education begins. It not only contains important information for the patient, but it also serves as a tool to assist the prescriber in discussing this important information with their patients. Some of the information contained in the PMIS is a general description of long-acting opioids, why they're prescribed, common side effects, medications and substances to avoid when on these medications, correct storage and disposal of the products, the importance of not sharing these products with others, and what to do if too much medication is taken.

The pharmacist material includes a dear

pharmacist letter which would highlight safety risk of abuse, misuse, overdose and addiction for these opioids and also include instructions for the pharmacist to dispense the medication guide with each prescription. In addition, the dear pharmacist letter would also be mailed to consumer medication information providers like Medi-Span and First DataBank to make them aware of the information within the REMS. It's also important to note that all of this information will be available to pharmacists through a website.

Licensing authorities and relevant associations would also be sent information. We believe that these boards could be very useful in our attempts at promoting education through their membership newsletters and other communications within their jurisdictions. Most licensing boards, they require certified education, and we think that the long-acting opioids could be one such topic that they could cover with these educational requirements.

Examples of boards that we would reach out to include the states board of medicine, pharmacy and

nursing, the Federation of State Medical Boards and the National Association of Boards of Pharmacy. The list of associations are too numerous to list here but include many professional organizations and also patient groups. We see these alliances with the associations and groups as an extremely important factor in helping IWG and the agency distribute a unified message about long-acting opioids.

The next component I would like to discuss is the elements to assure safe use or ETASU. FDA is proposing voluntary training, and our proposal for implementing an educational or training program is through the use of an extensive training guide, which we have submitted to FDA for review. This would be mailed to known prescribers and available to others. Also included in the training guide is a confirmation form, which would be returned by the prescriber attesting to having completed the educational program. These forms are important for the evaluation and tracking of the program. It allows one to evaluate how it is received by the medical community.

Prescriber training would educate

prescribers about appropriate patient selection, dosing and patient monitoring and also help them counsel patients on the safe use, storage and disposal of opioids. The prescriber is in a unique position to counsel the patients since they are in direct contact with the patient or their caregiver and are often seen as an important source for information. To that extent, we agree in prescriber education and have developed a training guide that addresses these important topics related to the prescribing of opioids as well as training confirmation form previously mentioned. But we also believe that prescribers should be able to receive continuing education credits for this training, which can create issues with accrediting bodies.

Knowing that the direct involvement of industry in the development of educational programs will not allow for CE credits and also knowing that FDA wants to approve any such educational materials, we propose that the agency review the educational topics and materials that were put forth by IWG and perhaps use these topics as a criteria for a, shall we

say, core curriculum for long-acting opioid training. That in turn could be developed with the blessing of ACCME or other accrediting bodies into an acceptable educational program in which prescribers could be incentivized to participate by obtaining continuing educational credits.

A lot of thought and work has gone into the educational components of the training guide, and some of the major topics include patient selection, appropriate dosing and the need for counseling patients on the safe use, storage and disposal of these products.

The encouraged use of the patient healthcare provider agreement is also included in this guide. No particular agreement is endorsed, but prescribers could use one of the many samples available online or through one of the learned societies that fits their particular practice or their needs.

When considering the goals of this REMS and that so much of the problem with addictions and prescription drug abuse is related to problems outside the influence of industry and the agency, it becomes

apparent that an area where we might have some influence, prescriber training, is an extremely important part. Voluntary training may work when done in conjunction with ongoing patient communications from other stakeholders, communicating a unified message on many different fronts; again, a multi-prong approach.

These educational efforts for the prescribers would mainly be assessed and tracked through the prescribers voluntarily cooperating and returning confirmation forms. And if the agency would determine that voluntary prescriber training is not working or that it is inadequate and some sort of required training is needed, then other options would be considered, perhaps using DEA registration as a means to ensure compliance.

This option was not initially accepted by our prescribing colleagues at the stakeholder meeting, but it was less objectionable than a new prescriber registry, which was flat-out rejected. The IWG has further investigated the option of using DEA registration as leverage in ensuring compliance with

an educational program with both DEA and congressional staff. However, if this option would be considered, it would take more time and more effort to pursue it.

This slide here shows a mockup or a prototype of what would be an opioid info website, and it would contain all the educational information and training materials available through this opioid REMS. This website would be an important resource for anyone seeking further knowledge about the REMS. And this particular one we have up here is for healthcare professionals, and you can see there would be multiple links to other areas that they might be interested in, whether it be training or whether it be the patient medication information sheet or whatever. It's also important to note that we would suggest having a toll-free number in which people can obtain additional information.

In conclusion, for this portion of the presentation, components which are included in the IWG proposed REMS are medication guides, preferably three, one for orals, one for transdermals and one for methadone; a communication plan which reaches out and

informs prescribers, dispensers, licensing boards and stakeholder associations about REMS and where more information can be obtained; voluntary training for prescribers under the elements to assure safe use, which includes training guide and training confirmation form; and we also included in the ETASU the patient medication information sheet, which serves not only as an educational piece for the patients but also assists prescribers in conveying this important information to the patient.

I'd like to thank you for your attention, and I'll now turn the mic over to Dr. Paul Coplan who will be discussing the assessment portion of this REMS.

DR. COPLAN: Good afternoon. Thank you for this opportunity to address you. My name is Paul Coplan.

The REMS assessments are designed to assure the ongoing effectiveness of the REMS implementation. They include studies and metrics to evaluate progress in distributing the REMS materials, to assess the impact on knowledge and in prescribing practices, and

to assess the impact on serious adverse outcomes.

The IWG metrics team has been working for the past year to develop the REMS assessment plan. The resulting assessment plan includes metrics that are designed to be both rigorous and feasible. The metrics are based on the objectives of the REMS.

The objectives of the REMS consist of two categories, objectives for education and objectives for measurement. The objectives for education are to inform patients, to inform dispensers and prescribers, and to train prescribers. The objectives for measurement are to assess patient and prescriber knowledge and awareness; conduct surveillance for abuse, misuse, overdose, addiction and death; assess shift in prescribing and associated outcomes with potential shifts in prescribing, and evaluate if the REMS meets its goals. And if it doesn't, to modify it appropriately based on the metrics.

The metrics the team proposes are very similar to the targets for metrics that the FDA has proposed. The REMS metrics proposed by the FDA in the proposed REMS document of the 28th of June states that

the metrics for the REMS will include process measures; measures of patient and prescriber knowledge; certain behaviors such as nonmedical use of prescription opioids; adverse events such as unintentional overdose, addiction and death related to prescription opioids; and finally, access to care.

To consider the assessments proposed by IWG, it is helpful to review the data sources available for the class REMS assessment because the selection is influenced by what data is feasible to collect or obtain. And this task is made much easier by many of the excellent presentations that were presented earlier today by experts in the various data sources.

In an ideal world, the drug safety databases that are used to assess safety risks for drugs in other therapeutic classes would be employed for this REMS. However, safety databases focus on the use of drugs by patients. An important risk associated with this class of products is abuse by non-patients. Therefore, a drug safety database that captures adverse events resulting from abuse in non-patients would be ideal.

In practice, claims and electronic medical record databases have inconsistent practices in coding overdose and the causal drug associated with overdose accurately for patients, even more so for non-patients.

One of the issues, I think, was referred to by Dr. Anderson with ICD-9 codes, which is typically what's used in these claims databases, ICD-9 Code 965.09, the code for opioid overdose, but it doesn't specify which opioid. There are separate ICD-9 codes for overdose with methadone and overdose with heroin and cocaine but not within the various opioids. So that complicates the evaluation.

Other challenges with available data are that there is a stigma associated with diagnosing a patient with an overdose due to nonmedical use of opioids. Events occurring due to nonmedical use may not get physician reimbursement for their work, so they may alter the claims code to enhance the chance of reimbursement. For non-patients, it is often unknown what drug the individual was taking. And the databases don't record causal drug associated with

overdose in a standardized way, so this is often not available in the records.

Another ideal data source would be one that documents emergency department visits for nonmedical use of opioids that has a stable set of emergency department centers that participate in the study over time; that is, a stable sampling frame. Ideally, ED visit data would record the specific opioids that the patient was exposed to and whether the formulations were those included in the class REMS; that is long-acting formulations, or those not included in the class REMS, that is, immediate-release formulations.

DAWN, the Drug Abuse Warning Network, is a federal government-funded study that does measure emergency department visits for abuse. And as Dr. Dormitzer showed earlier, it is a good source for monitoring ED visits for nonmedical use of opioids. But the sampling frame has shifted over time as the number of participating ED sites has varied.

In addition, while data has been available in the past from DAWN, the parent agency of DAWN, SAMHSA, has recently decided that the data from DAWN

cannot currently be provided to sponsors of products. Hopefully, the availability of DAWN data to sponsors will change soon.

An additional challenge of DAWN is that many ED visits are associated with people taking several concomitant prescription opioids, illicit drugs, alcohol, or other drug classes such as benzodiazepines concurrently. So the primary causal drug or the mechanistic interaction of several drugs are difficult to discern. And that was apparent from the data that Dr. McLellan presented earlier, where in the two cases series of deaths, one by Dunn and one by Hall, et al, concurrent taking of a benzodiazepine was a big risk factor for an overdose death. So determining what's the primary causal drug in that situation is complicated.

Additionally, forensic toxicology testing usually identifies active drug substance rather than formulation. Mortality data is also complicated, as are ED visits, by the frequent presence of multiple opioids, illicit drugs and other CNS-depressant drugs, making determination of the primary causal drug

difficult. And no widely accepted standard operating procedures exist to help the medical examiner or forensic toxicologist make this determination.

Surveys of reported abuse that capture long-acting or immediate-release formulations for all drugs would be ideal. In practice, most surveys, including the NSDUH survey and the Monitoring the Future study that we heard about earlier today, don't differentiate between long-acting and immediate-release formulations in the questions asked, with the exception of one or two active drugs substances. One exception is for oxycodone.

If the questions are asked in the survey, they're often not included in the reports that are made available to the public, which is the access to the survey data that the sponsors have.

The REMS assessments proposed are designed to provide feasible and rigorous metrics for each of the objectives. Because there's no one single ideal data source, a mosaic of metrics is proposed where each piece of the mosaic provides some useful information, but it takes multiple metrics to begin to

see the big picture.

These are the objectives that we have developed to meet FDA's target metrics. The first objective is to inform patients. This is an educational objective. The REMS tools that will be used for this objective are the medication guide and the patient medication information sheet or PMIS. The evaluation will be conducted by means of a patient survey.

The REMS assessments will evaluate the following metrics: First, a comprehension testing of the med guide and the PMIS by interviews and focus group discussions to ensure that patients understand the content of these materials, and the tools are optimized for the purpose of simple, unambiguous messaging.

The second metric is a process measure, the number of med guides mailed or downloaded. The third metric is a patient survey to assess patient knowledge and awareness about the important information contained in the medication guide and, also, whether or not the patients received the medication guide.

The second objective is to inform dispensers and prescribers about the risks and safe use practices. This is an educational objective. The REMS tools that we'll use for this objective is the dear healthcare professional letter that will be sent to prescribers and dispensers, all 700,000 of the prescribers and 260,000 dispensers.

The metrics to assess this objective are the number of the dear healthcare professional letters mailed and the number of dear healthcare professional letters downloaded from the Internet from the class REMS website where all the REMS material will be posted and made available for downloading.

The third objective is to train prescribers about the risks and safe use practices. This is an educational objective. The REMS tools that will be used to achieve this objective are the training guide that will be sent to prescribers and will be available online through the REMS website,. either as a downloadable PDF file for printing or reading online or as a online training program.

The metrics to assess this objective are the

number of training guides mailed and downloaded from the Internet, the number of confirmation forms completed by mail and Internet by prescribers to confirm that they have taken the training, and the level of prescriber knowledge. The assessments will also evaluate training coverage by comparing number of training guides provided and confirmation forms completed against the number of training guides mailed in the universe of Schedule II prescribers.

The fourth objective is to assess patient-prescriber knowledge and awareness of the risks and safe use of these products as described in the medication guide. This is a measurement objective. The REMS tools that we'll use to achieve this objective are REMS surveys of patient and prescribers that will be conducted to evaluate the level of patients' and prescribers' knowledge and awareness. These will be done by a third party that are not generally -- to address the previous question, by a third party that is independent of industry and generally a nonprofit group.

The metrics to assess this objective are

patient and prescriber knowledge. Sample sizes will be sufficiently large to be adequately powered for stratification by four geographic regions and by the prescriber's training degree such as specialist versus primary care provider, nurse practitioner or physician's assistant.

One of the issues we discussed within the IWG is did we want to target high prescribers or occasional prescribers, and we obviously decided that it was important to focus on both. And these surveys would target both type of prescribers because getting the message to both types is important.

The fourth objective is to conduct surveillance for abuse, misuse, overdose, addiction and death. This is a measurement objective. The REMS tools that we use to achieve this objective are surveillance studies. The REMS assessment will consist of the following: emergency department visits to measure changes in overdose rates, poison control center exposure reports to measure changes in the rates of unintentional adverse outcomes resulting in poison center reports, patients entering drug

treatment facilities, adverse event reports as evaluated through FDA errors, surveys that reported abuse in teens and adults using the NDSUH and the Monitoring the Future surveys. However, it is important to note that these surveys do not separate longer-acting versus IR formulations for the majority of products included in the class REMS. And lastly, mortality data obtained through the National Vital Statistics collected by the federal agencies and the National Center for Health Statistics within the U.S. CDC and the National Vital Statistics System.

There are multiple metrics for the surveillance of abuse, misuse, overdose, addiction and death, and each has an associated data source. In this summary figure, the left column of boxes represents various outcomes of interest, and the right column of boxes represents sources of information on the outcomes. So, for example, emergency department visits will be assessed through DAWN, poison center exposures through the poison control centers either through the American Association of Poison Control Centers or the RADARS, patients entering substance

abuse treatment by the RADARS system or the NAVIPPRO system, adverse event through FDA errors, abuse rates in teens and adults through the surveys, and deaths through the National Vital Statistics System. Addiction would be measured through patients entering substance abuse treatment and through various fields on dependence available in the NSDUH survey.

This sixth objective is to assess shifts in prescribing and associated outcomes. This is a measurement objective. The REMS tools that were used to achieve this objective are claims database studies to assess shifts in prescribing and the surveillance studies previously described to assess possible adverse outcomes.

The REMS assessments will consist of the following: shifts in prescribing using claims database analyses from prescriptions for class opioid analgesics to non-class analgesics such as short-acting opioids as well as prescription and nonprescription NSAIDs; shifts in associated adverse outcomes using the surveillance studies described. The most useful data sources for this purpose will be

the poison center reports for class and non-class analgesics and DAWN since there's clear differentiation between class and non-class formulations of the active drug substances in these surveillance systems.

The seventh objective is to evaluate whether the class REMS meets its goals or should be modified. This is an evaluation objective. The REMS tools that we use to achieve this objective are meetings of an external review advisory board of independent medical and scientific experts as well as a sponsor management group that will continue to manage the implementation and possible modification of the REMS.

The REMS assessments will consist of an integration and evaluation of all the REMS assessments mentioned above.

Each of the seven objectives of the proposed class REMS has an associated set of tools that will be used to achieve the objectives as well as an associated assessment to evaluate the impact of the tools in meeting the objectives. It all fits together as a whole as shown in this table that is included in

your handouts and in the REMS supporting document of the IWG proposal that was submitted to the FDA two weeks ago for more detailed perusal at your convenience.

DR. KIRSCH: For those of us who have handouts, it's on page 40.

DR. COPLAN: A comparison of the target metrics proposed by the FDA for the class REMS and the IWG proposed assessments of the REMS shows a good agreement between the two. There is assessments proposed by the IWG for each of the FDA's target metrics. Perhaps the most difference between the two metrics is in the area of access to care. Since it is difficult to measure how many patients who need to get longer-acting opioids are not able to access them, we've proposed a more feasible metric, which is shift in prescribing, particularly in patients who are already on longer-acting opioids and switch to shorter-acting opioids. What we would be looking at is a change in the rate of shifting from long-acting to short-acting at the time of the introduction of the REMS.

The FDA proposed using the Medical Expenditure Panel Survey, as Dr. Willy discussed earlier, and this is a set of large-scale surveys of families and individuals, their medical providers and employees across the United States to assess access to care. And this is something we can look into using.

While developing the class REMS proposal, the IWG and other groups have made progress in collecting some baseline measurements. Available data for guiding the class REMS assessment plan are data that has been collected on qualitative research on the patient materials with particular focus on educating patients on the symptoms of overdose. In addition, baseline data from the National Poison Control Center and the NSDUH survey are available.

The report providing baseline rates of U.S. poison center mentions for products included in the class REMS between 2006 and 2009 has been submitted to the docket by the RADARS system. A key point is that the baseline rates for class opioid is established and has been reasonably stable over the past few years, at least the trend has been reasonably stable.

Similarly, the comparator baseline rates for non-REMS opioids has been established by the National Poison Control Center reports, and these two have had a reasonably stable trend over the past few years.

In the NSDUH survey, nonmedical use of pain relievers among people 12 years of age or older in the U.S. between 2002 and 2008 has identified a stable trend over time; for example, approximately 2 percent of the U.S. population reporting nonmedical use of opioid pain relievers in the past month in 2002 and 2008, as it was mentioned previously by Dr. Conway.

Similar stable trends have also been found with nonmedical use in the past year. However, the rates of reported nonmedical use by class and non-class REMS opioids cannot be evaluated from public NSDUH reports. These data indicate that there are established and relatively stable trends in rates in place for many of the data sources. Post-REMS rates will be compared to the baseline rates.

So this is a slide for those in the audience who didn't have the slides. This is the slide that shows the integration for each of the seven

objectives, what are the REMS tools and what are the assessments that will be used to evaluate whether those tools are meeting their REMS objectives. And finally, the seventh objective is to assess all of the metrics. And if the metrics indicate that the objectives are not being met, to iteratively improve the REMS tools so that we can achieve the target of the REMS.

We tested the full text of the medication guide and the patient medication information sheet in in-depth interviews with 20 patients taking long-acting opioids, 10 primary care practitioners, 10 pharmacists and 10 nurse practitioners and physician's assistants. An example of the med guide text we tested is the following. "Long-acting opioids can cause serious breathing problems. Slow or shallow breathing are signs of a life-threatening overdose. If you or someone around you is experiencing any of these signs, seek emergency medical attention right away by calling 911 or your local emergency services."

One of the primary risks with this class of medication is the adverse event resulting from an

overdose of the opioid analgesic. A little bit of agonist effect on the opioid receptor reduces pain. A little more agonist induces a euphoric effect, and still more agonism results in profound sedation and respiratory depression. Due to the development of tolerance in a patient, the dosage levels that reduce pain and induce a serious adverse event change depending on how long the patient is receiving the drug for.

The adverse event is insidious because the patient doesn't realize that he or she is stopping breathing. Further, family and friends mistake the sedation from overdose as the patient sleeping and therefore fail to call medical attention to the patient in need of urgent medical care. An additional characteristic of this adverse event is how easily reversible it is with an opioid receptor antagonist such as nyloxin.

This is perhaps the most reversible of serious drug-related adverse events, and this needs to be a cornerstone of any risk management plan. And presumably, because it is so reversible, education

could have a major impact on this serious adverse event if the education does reach the people who are at risk.

It is therefore vital to communicate this message clearly to patients and their family members so that if patients experience an AE, it is recognized quickly by family members or caregivers and emergency help is summoned as soon as possible. Alternatively, the patients would recognize the AE in family members or pets who may have ingested the patient's medication.

Selected findings from the interviews are that physicians and pharmacists admit not spending time with patients to discuss signs of overdose. Physicians and pharmacists agree it is important to inform patients and caregivers in the case of an overdose in the patient, family member or pet and to inform family members so they can be alert for the signs and symptoms in patients.

Most patients do not recall their pharmacist or physician discussing what to do during an overdose. One patient summarized the impact of reading this

medical guide text as, “This is not your average painkiller. This is the big league. If you take too much of it, they’re going to be problems.”

The IWG proposed REMS includes both a medication guide for patient education via pharmacists and the patient medication information sheet for education by prescribers to ensure that this message is communicated to patients and in the training guide for prescribers, in the elements to assure safe use, to ensure prescribers are aware of this information and the importance of communicating these messages to patients.

However, it is noticeable that this communication would not go to non-patients who would be vulnerable to the lack of knowledge. And one of the things that Dr. McConnell pointed out was how a quarter of the patients in both the Hall study and the Dunn study had had a previous emergency department visit for overdose; hence, an opportunity to educate patients about the nature of the adverse event that would not be realized by handing the medication guide out to patients who are prescribed the drug.

In conclusion, the IWG proposes that the assessments measure the effects of the REMS tools on the objectives, including distribution of educational materials, receipt and completion of education, level of knowledge, and impact on serious adverse outcomes. Data will be interpreted by the external expert advisory board and the sponsor group. Recommendations for modifying the REMS based on the assessments will be made by the external expert advisory board and the sponsor group. The IWG's proposed assessments are consistent with the FDA's REMS.

Lastly, the IWG is committed to work with FDA to improve data sources to better assess REMS outcomes. We recommend that this is done in a pre-competitive way along the lines that some of the biomarkers have been developed in a industry consortium, in a public-private partnership, which has been successful in avoiding any kind of partisan issues with any particular company and has been successful in improving the science on which good drug development and safe use can be affected.

The intention of this effort is to provide

the best feasible scientific assessment of the serious public health problem. This work is designed to mitigate the risk to patients and the burdens of abuse, misuse, diversion and unintentional exposures thereby enhancing the benefit-to-risk balance of long-acting opioids. Thank you for your attention.

DR. KIRSCH: Thank you.

Our next speaker is Dr. Herbert Neuman from Covidien.

DR. NEUMAN: Good afternoon. I'm Herbert Neuman, vice president of Medical Affairs and the chief medical officer for Covidien's pharmaceutical segment. I appreciate the opportunity to share our experience in managing the risks of Exalgo, a long-acting opioid. Over the last few months, we've deployed the Exalgo REMS and have more than 60 voluntary tools and programs in development. I'd like to tell you about what we've learned through these efforts.

First, I'd like to say that Covidien agrees that the long-acting opioid REMS proposed by the FDA appropriately addresses the fundamental requirements

for this class of analgesics. To be successful, any REMS must strike a balance between the requirements of patient safety, access to needed medications, and prescriber choice of appropriate analgesics. But this should be only the beginning. To achieve this goal, pharmaceutical sponsors must evaluate each product's individual risks and benefits. Implementation of the class-wide REMS should be augmented by voluntary tools for each product that exceed the required REMS elements. The responsibility for patient safety is shared between sponsors, regulatory agencies, prescribers, office staff, dispensers and patients. Covidien embraces our role in this shared responsibility.

To provide context for Covidien's experience with Exalgo, we've noted here the approved indication for the product, which launched in April of this year. The Exalgo REMS is identical to the FDA proposed class-wide REMS except for these additional elements, class- and drug-specific language in the medication guide and patient education. So our experience in administering the Exalgo REMS provides insights into

how the FDA proposal can be applied.

At Covidien, we're applying a scientific approach to the mastery of risk management. Prior to Exalgo's approval, we conducted an extensive failure mode and effects analysis, or FMEA, of the medication use process around Exalgo. This evidence-based methodology addressed both process failures and the corresponding causes. It identified a range of mitigating tools. These tools were refined and validated by multiple stakeholder focus groups.

As a result of this analysis, we plan to deploy more than 60 voluntary tools. Here's a view of the required Exalgo REMS elements versus a sampling of the voluntary tools and programs we're implementing.

Our real-time experience with the Exalgo REMS provides valuable insights. One required element of the REMS is an assessment of the education program. We used the Exalgo essential information form, or EEIF, for that purpose. We received voluntary EEIFs from numerous healthcare professionals. After evaluation of these submissions, we were alerted that many actual prescribers still need to complete this

assessment.

Fortunately, we anticipated this possible result through the FMEA process. Even before our product launched, we created a mailing to 60,000 potential prescribers. Ongoing, we have a call center contacting every single prescriber who still needs to complete the EEIF assessment. Our commercial team is encouraging submissions, and our medical science liaisons are prepared for individual conversations if needed. This process targets 100 percent participation by prescribers of Exalgo.

As noted previously, the FDA has included patient education in their proposed REMS for long-acting opioids. We completely agree with that focus. One of the voluntary tools that we've put in place for Exalgo is a patient kit, which we've shown here. The kit includes a brochure that answers many common questions and provides guidance on the safe use and storage of the product. It also includes a pain diary and an introductory video.

As a result of that FMEA process, we learned that patients can easily forget when they last took a

once-daily product. So we've provided a dose alert timer that gets placed on top of the pill bottle. The sound of the alarm reminds patients when it's time for their next dose. This will help address unintended overuse as well as under-treatment.

Through a continuous improvement process, we can find the combination of education and other tools that will maximize the benefits and minimize the risks of this important class of medications. Our internal oversight team measures the performance of our REMS. We've established an expert advisory board to provide commentary and recommendations for improvements. We have planned ethnographic studies of experts in the field to identify original risk mitigation methods that we can bring to a broader prescriber audience.

At Covidien, our focus is on mitigating the risks of our products. We support this philosophy through three pillars of effective safe use initiatives, collaboration, education and innovation. The FDA has proposed a REMS that is appropriate and well balanced to meet the needs of patient safety, access and choice. And that is an essential

foundation, but the pharmaceutical industry must take responsibility for developing supplemental voluntary safe-use programs tailored to the unique risk profiles of their products.

We hope our recent experience provides you additional context as you consider the class-wide REMS. We also hope our philosophy helps you establish appropriate expectations for all manufacturers of long-acting opioids. Thank you.

DR. KIRSCH: Now we have time for any remaining questions. This part of the agenda will last no later than 5:00. So the next person to ask a question is Dr. Farrar.

DR. FARRAR: I have two questions, just to try and draw attention to a couple of issues. We've heard a fair amount today about metrics, and I actually wanted to ask Dr. Anderson -- if he's still here; probably not. But I will continue with it because I think it's worth following up on.

I can ask Dr. Coplan to address this issue, actually, which is that one of the issues about measuring anything is understanding that the outcome

is actually real. And, certainly, a lot of the metrics that were suggested to us today, in the suggestion of those metrics, I heard nothing about any data related to whether they actually demonstrated the risk or benefit that they were meant to measure.

Taking the most obvious one which is death due to opioid overdose, I wonder if Dr. Coplan could perhaps address in Dr. Anderson's absence the issue of trying to differentiate a death due to opioids versus a death in the presence of opioids, which clearly will be an important metric for judging whether any of these projects work. And then I have one other question.

DR. COPLAN: Thank you, Dr. Farrar. This is clearly a major issue, and as mentioned, we do not have a protocol for consistent determination. I think one thing we would look to -- what we would recommend going forward, since one of the topics for discussion is how to improve data sources to continue evaluating the outcome of the REMS, is that my personal history is in developing vaccines and HIV drugs. And in that environment, any infectious disease, such as HIV but

even streptococcal pneumonia infection, or even a varicella infection, is reportable to the CDC.

As we heard earlier as something that's for prescription drug overdoses that's the number two cause of death in the United States, that seems disproportionate that we don't have a national reporting system to the CDC for overdose deaths, which would circumvent a lot of the state issues that Dr. Anderson was referring to. So I think that would be a relatively easy fix, and I think the way to do it is to do it, as mentioned.

One of the things Dr. Woodcock has spearheaded in CDER, which has made a big difference to developing the signs of safety biomarkers is, as mentioned, the Critical Path Initiative where biomarkers are developed. And the basis for that, according to Dr. Woodcock, was that if drug company X is developing a drug, and as part of that they have to monitor for liver disease, and they develop a biomarker for early detection of liver disease, that company has no credibility. That biomarker will never be believed because it's always presumed that that

company has a perverse motive in developing that biomarker.

So it has to be done in a public-private partnership where the resources and the motivation, the drive, can come from the groups within society who are tasked with developing new drugs, the sponsors and the regulators and academic experts. So I think that's where we need to go.

The question, of course, for where we are right now is that if we introduce a new REMS in over the next period of time, we would need to have a baseline to compare to. And so that would be the challenge. We'd have to use the current data, and I think that's where we -- the discussions we've been having in the metrics team within IWG is that probably what we'd not be able to get at generalizability across the United States because of the inconsistency of quality. We'd probably have to pick specific states where there is better quality. Dr. Anderson mentioned some of them like New Hampshire, Utah, and perhaps look within a few states; do we see changes in mortality?

But nevertheless, we will still be stuck with the limitation that we won't be able to differentiate between REMS and non-REMS opioids, which is a pity because it provides a good comparator, and that the multiple causal drugs -- the protocol for determining which drug is primarily causal, this is merely an innocent bystander or perhaps a minor contributor. So the continuum of causality would not be defined in any standardized fashion.

DR. FARRAR: Thank you. The point that I think Dr. Coplan made quite well is that as the REMS are developed, it's not simply about developing what measure we're going to use and how it's going to be used. I think a vital piece is to instill into the whole program measures which will allow us to judge the quality of the measures we're using. And that's a research agenda, but really, if it's not built into the program, you're at risk for getting data that's of no use ultimately in deciding if the REMS is useful.

The second question, which I was going to address to Dr. Weiss, and I guess it could also be addressed to Dr. Neuman in terms of specifics, one of

the things you indicated in your contract was the need to indicate that you shouldn't sell, lend or give your opioids.

It seems to me that the opioids are much closer to a gun than they are to other things in terms of the way they should be approached. And one could argue that you ought to prevent access as well. And I would simply ask the question of whether you think that that's an important thing perhaps to add to the contract, that people ought to store them in a way that prevents accidental access.

DR. WEISS: I think there's been many who have commented on this issue about proper storage, particularly as it relates to young people having access to the medication in some of the data that were shown earlier about where the misuse and nonmedical comes from, has been this issue of appropriate storage and minimizing the intentional exposure because things are not locked up, not appropriately disposed of, et cetera.

So when I presented the provider agreements, or contracts as you call them, this was just put out

there as one potential activity that could be developed and explored should there be sort of uniform consensus that enhancing patient-provider agreements would be a good activity to undertake as part of our Safe Use Initiative, and then we'd want to have more input from interested parties on what should be contained in them and for the people that would be using them, what kinds of elements and what kinds of messages would be important to put in there.

I think as well for the educational campaign that we were talking about and some of the partners that we would work with, an overriding message would be the issues of safe storage and keeping medication, this class in particular but others as well, out of reach of individuals for whom there might be some intentional or unintentional type of harm.

DR. FARRAR: And I wonder if I could ask Dr. Neuman to address whether any of the material they have actually talks about locking up the medication so that -- it's never your son who's going to take it, but if you convince patients that it's the friends of your son who are going to take it, then they're much

more cooperative.

Dr. NEUMAN: Yes, our patient kit does have information about proper storage. It talks about -- actually, I'm going to take a step backwards. Really, our assessment of what's going on out there right now is before we start talking about storage and locking things up, I think patients would really benefit from realizing how desired, how valuable the opioid is to begin with.

We saw the statistics earlier this morning where the vast majority of abused opioids come not from street-level dealing or from Internet pharmacies but from a friend or a family or a doctor, whatever. And that's really the first step of education. Before you start getting into tactics around what to do and how to do it, we would really advance the agenda if we could just make people aware of the danger in a broad sense.

DR. FARRAR: So the answer is no?

DR. NEUMAN: It is part of our patient education kit. Proper storage is part of our patient education kit, and advice to physicians to coach

patients around proper storage is on there. But again, it's focused more on just awareness of the danger as opposed to specific tactics.

DR. FARRAR: I understand, but it doesn't say it should be locked up as opposed to I keep it in my sock drawer, which is what I usually hear.

DR. NEUMAN: It says being kept away from people who might take it. We talk about the types of people, including service people who might come into the home and that sort of thing.

DR. KIRSCH: Dr. Deshpande.

DR. DESHPANDE: The proposed REMS relies heavily on education, and I have a question for our ACCME presenter, Dr. Kopelow, if he's still here. Two questions, one is what is the decrement on average of an ACCME learned content.

DR. KIRSCH: I think he's not here.

DR. DESHPANDE: He's not here. So I will reserve that. I hope he's around because I think the two issues I have with that is that every educational program has an uptake of knowledge, which is then decremented over time, and we don't know what that

decrement is. And secondly, a practice change is difficult to demonstrate. And Dr. Vlasses may be able to help us if he's here. If he's not, then I'm not out of luck.

DR. KIRSCH: Dr. Wolfe.

DR. WOLFE: This is a question for Dr. Rappaport for his 1 o'clock presentation as opposed to his three others today.

You mentioned at the beginning of your presentation that the FDA -- and I think it's for very understandable reasons, resources and everything -- decided not to include in REMS the electronic verification of doctor training. You then later in slide 7 mentioned that legislation to link this to DEA registration would be something that would need legislation, which is clearly the case.

Do you support that legislative effort? And the follow-up question would be, would you like our opinion on that?

DR. RAPPAPORT: I'm going to ask Ms. Axelrad to address that question.

MS. AXELRAD: I think, as you know, we're

really not authorized to comment on whether we would or wouldn't support legislation without going through the process of vetting that through the administration. It has to go through a process. But we certainly would welcome the committee's views on whether they think that would be helpful.

We also identified in our background document, and Dr. Rappaport identified during his talk, that while that might be over the long term a more efficient way of making sure that prescribers have training, it would require legislation. And so we do view it as a longer-term out there solution. That is, even if we were to support it, by no means certain that we would actually be able to get legislation to implement that.

DR. KIRSCH: Dr. Krantz.

DR. KRANTZ: It's been a while, I had a number of questions. One quick one, because when we were talking about the death information, I wasn't super clear on the sort of baseline incidence. And we saw some nice data from Dr. Dormitzer on retail prescription adjusted rates for ER visits.

What about for death, do we have that data at all?

DR. KIRSCH: She's shaking her head no.

DR. DORMITZER: No, I don't have deaths adjusted for prescriptions.

DR. KRANTZ: Are there other data sources we could look at? Let's say the CDC, for instance, look at sort of baseline rates of death per year for the opioids and then specific the different products?

DR. DORMITZER: I'm not sure. I still have to -- at this point, I have to say I don't know. But to do death over prescriptions by state, we've done it with the DAWN mortality data. And so yes, we could go back and do that.

DR. KRANTZ: I just think it's important to give a context for what we're deciding here from a public health perspective.

DR. DORMITZER: Yes. Now, what we could not do, though, is formulations. So it would be hydrocodone, oxycodone.

DR. KRANTZ: Sure.

DR. DORMITZER: But I would have to get more

information on the medical examiner data piece of it.

DR. WILLY: If I may, I have a publication. This is from NCHS, which is part of CDC, and it shows poisoning deaths. But it is only the numerator. It shows an increase, and it does not provide it for specific drugs, but it does show an increase from 1999 to 2006.

DR. KRANTZ: So, for example, when we look at the medications in the briefing documents, there was 14,000 deaths in 2006, I believe. That was not -- we can't break that down into which medications that constitutes, those 14,000 deaths?

DR. DORMITZER: No -- with the ICD-9s -- ICD-9s, no, because it's opiates. DAWN does have more ME data by -- and I think they have it complete for six states.

Like I said, it would just be the substance; it would not be anything more than that. So we could go back and look at that by state deaths over state prescriptions, but it would not be by formulation. That, we absolutely would not be able to do because that type of data is just not collected, and I think

it also depends on the tox screen. But let me look at that. Yes, I can look at that.

DR. KIRSCH: Can I ask that when an individual comes to the microphone that's not on the committee to please state your name before you begin to speak.

Next is Dr. Todd.

DR. TODD: I had a question for Dr. Rappaport. This goes back to the 1 o'clock presentation again. I was confused about the question of exempting certain specialties from the training requirement and FDA thoughts around that. Certainly, as an emergency physician, we rarely prescribe long-acting opioids from the department, but various specialties have complementary roles to play. And I'm trying to understand how the training requirement might apply to us. And just as an example, although we may not be prescribing these medications often, we're very often dealing with the consequences and the outcomes as evidenced by our frequent referrals to DAWN data. And I do think we have a role to play in identifying complications, identifying issues related

to safe storage, diagnosing prescription opioid abuse and providing intervention.

So what are FDA's thoughts around the exemption for specialties, hospital-based physicians exemptions, and, personally, I'm interested in the emergency department issue.

DR. RAPPAPORT: Yes, I'm sorry if it wasn't clear today. But I think even though we haven't finalized our thinking on it, I think we're mostly in agreement that there really aren't any disciplines, with the possible exception perhaps of pain medicines, board certified pain medicine specialists, who should be exempted. Because in any specialty, at some point you're going to be either prescribing or dealing with the consequences of these drugs, whether as an inpatient specialist or an outpatient specialist or a generalist.

So really where this came from was that some of us thought, well, many of the people around this table are experts in using these and was there some way that we could exempt you-all from it. And it's a hard thing to do, so I'm not even sure we would

ultimately want to exempt anybody. But if it was to be anybody, it would probably be board certified pain specialists.

DR. KIRSCH: Dr. Porter.

DR. PORTER: I had a logistical question for the IWG group, perhaps Dr. Coplan.

In their communication plan under the REMS, there would be many different mailings out to the prescribers and then there was also mention for some of the outcome measures, perhaps to a third party, that patient surveys would be done. So that requires that there's a database for the physicians, a database for the patients that perhaps includes even some of the data on their behavior.

So where are those databases currently held, who has access to them, and would that change under the REMS?

DR. COPLAN: First, let me say that the communication plan would consist of one mailing. So all the materials would be mailed in one packet and perhaps repeatedly, but the physician or prescriber wouldn't be getting lots of mailings. The surveys

would be done separate from that, several months after people had gotten the package to evaluate the level of knowledge, and there would be a random sample.

So the question of the databases, are you referring to the database which is used to identify which physicians to mail to or can you clarify?

DR. PORTER: The physicians and for the surveys, the patients.

DR. COPLAN: So the survey of patients would be done by a third-party group, typically, a nonprofit survey group that would conduct the surveys, collect the data, and provide a report to the FDA, to the external advisory board and the sponsors.

DR. PORTER: Right, but where would the patient contact information come from and where would that information be held?

DR. COPLAN: It depends on how the survey -- how the sample is selected. One way that the samples are typically collected for this is to use primary care practices, large associations of primary care practices, and to invite patients who are receiving the relevant drugs to participate in a survey from

those primary care practices. So there wouldn't be a database -- so there's a database of the results. There's no database to target which patients to select.

DR. PORTER: Okay. So patient confidentiality was one of the concerns, so it shouldn't be an issue.

DR. COPLAN: No. Everything would be 100 percent HIPAA compliant and reviewed by any ethics review board, IRB, to ensure that that wouldn't be an issue.

DR. KIRSCH: Dr. Nelson.

DR. NELSON: Thank you. The good news is that most of my questions have been asked and answered already. But I do have one for Dr. Weiss, if I can.

Obviously, the Safe Use Initiative has good intentions. It's very heavily based on, I guess, education. But has the use of the patient-provider agreements been studied? We know that patients don't always "listen" to their doctors when they're given advice or instructions.

Is there data that actually suggests or

supports the idea that by putting the data on paper and having the patient sign it actually changes their behavior or influences their outcome? I mean, in my practice, I know that I routinely give discharge instructions to my patients, which are on paper and signed, and I know that the data to actually support that this improves anything is very, very flimsy.

So is this just really a little bit of a window dressing put-on an educational process or is there any real benefit to doing it?

DR. WEISS: I'm looking at a very nice summary in "Pain and Addiction Treatment" that actually addresses a number of issues related to written agreements. And I think the answer is probably yes. One specific data point or summary of these types of agreements in general highlights problems concerning the use of written agreement -- treatment agreements include very limited empirical evidence supporting their effectiveness and gives a specific reference to that statement.

When I presented patient-provider agreements as a potential area, I hope I made it clear that this

isn't something that we're saying we think is really the right thing or a right thing to do as part of Safe Use. It's a potential opportunity for partnerships. It requires a lot more research and input from experts like you-all and others to address whether it is a tool that might have some benefit. If it does, how to assess what we know about it right now, what existing data are available right now, how much more data should be collected if it is a route to go.

We need more input into these and other types of potential opportunities that might have an impact on this particular problem of appropriate use of opioid medications. So I think there are a lot more questions probably than there are answers.

There's a whole host of different types of agreements, and just pulling out a number of them, they're all called different things. They all have different elements in them. They have a lot of varied issues and concerns. And I think if we get feedback that this is an appropriate avenue to at least try to explore, then we really want to set up some series of discussions with experts to really hone in on this

particular aspect as a potential avenue to add on to other programs to maximize safety.

DR. RAPPAPORT: If I could just add in response to your question, there may be people who remember more about this than I do, and I don't have the data with me. There was an entire session at the American Pain Society meeting this year a couple months ago on how these programs are working, and the person who ran that session -- I only caught part of it, but I know she did draw some conclusions that they were showing significant effect in many areas across the country. And she also thought that because of that effect, the opioid REMS program from the FDA was not needed at all, which I didn't agree with.

But I think if anybody else was at that session at APS, you might want to comment on it as well, but there is clearly some data out there, and it's easily retrievable from the meeting.

DR. KIRSCH: Dr. Berger.

DR. BERGER: Actually, that's a good follow-up because I had the same question of industry. Today we heard from some of the speakers that there was

limited evidence of these agreements having any evidence that they were effective, and industry is making this part of the training. And if there is limited evidence that this is something that we should be using, we need to question whether this should be part of the training or is industry saying this is just one of the suggestions that -- I'm unclear whether industry is saying -- and this was Dr. Davis' suggestion.

Is this just a suggestion or is this what industry is saying we want? I don't really know.

Do you want to maybe comment? Because in some of the earlier lectures this morning, it was indicated that there was actually little evidence, and why are we recommending something that has little evidence? And maybe we really do need to go back to literature and not just go on one lecture by APS. We need to see is there a meta-analysis out there. I don't know. I haven't looked recently.

DR. HADDOX: Dave Haddox with the industry working group.

We heard from our stakeholders, basically

the long and short of it was there was not a consensus. There were some people that were very adamant that they should be used. There were some people who were short of wishy-washy. There were some people who were very concerned about the tone and the readability, the comprehensibility of it.

DR. BERGER: But what is the evidence? Is there evidence?

DR. HADDOX: We don't think that there is a good solid evidence base. So we are letting people know that there is a lot of learned societies that encourage this, and that's why we have not created one that we would propose as the one to use.

DR. BERGER: Okay. Because evidence is really what we should be basing --

The other thing for Dr. Rappaport, in terms of you had said pain physicians were the only physicians. Perhaps I would also suggest palliative and hospice care board physicians also. If you're talking about pain physicians' knowledge of opiates, palliative and hospice care boarded physicians would be up there, also.

DR. KIRSCH: Dr. Hatsukami.

DR. HATSUKAMI: This is a question for Dr. Coplan.

You had mentioned in your presentation that you're going to be examining the number of downloads for different materials like the medication guides and the trainer guides. And I was wondering whether it's possible to look at not only the number of downloads but the number of different prescribers that have downloaded the information. That's one question. And whether one can also look at the number of downloads that occur across different states so that it may be possible to link it to potentially the DAWN data or even the survey data that you'll be collecting.

DR. COPLAN: Well, we'll share that question between the IT team and the metrics team. So from a metrics perspective, the confirmation form that we're asking physicians to send back would have the state and the specialty. In terms of the download, that would depend on the person who's downloading it putting in that information.

MR. ALEXANDER: Justin Alexander from the

technology team of the IWG. We would not be expecting to collect personal information as a result of accessing this website. So we would be able to gather certain amounts of information as to who would go to those different pages and what they would access and kind of follow through as a funnel. But we wouldn't know any demographics or specialties. We wouldn't expect to know that.

DR. HATSUKAMI: Yes, I guess I wasn't thinking of personal information but just information collected by state, for example, just to be able to relate it to some of the epidemiologic data to see whether there's a relationship between the number of downloads by state and the number -- so that's primarily what I was thinking.

MR. ALEXANDER: Yes, and that could be done.

DR. KIRSCH: Dr. Bickel.

DR. BICKEL: I have a question about the industry group and the FDA. Dr. McLellan this morning talked about the relevance of socioeconomic status. That was confirmed by the representative of SAMSHA.

The relationship between socioeconomic

status and health behavior produces results that are generalizable, robust and simple. The lower the SES, the less likely to engage in health behavior, including listening to and attending to physician's advice. As such, it suggests that individuals from lower socioeconomic status will not be impacted by the same document that's produced and given to individuals of a higher socioeconomic status.

Given that, has either group contemplated developing or customizing the information so that it's relevant to the different populations?

MS. STANTON: Marsha Stanton from the industry working group. We have looked at various forms of the patient information sheet. We've looked at translating it into various languages, most importantly Spanish if we move forward with that particular sheet. But we've also in discussions amongst ourselves talked about various forms of the information sheet that could be utilized in various socioeconomic groups, aging populations, pediatric populations. We have not moved forward with it as yet because we're not sure that it will be a part of the

program as we're going forward.

DR. KIRSCH: The last question of the afternoon will be by Dr. Craig.

DR. CRAIG: Thank you. I had a question for Dr. Rappaport.

In your presentation today, you didn't discuss which was proposed earlier by the agency which would include pharmacy certification and/or training. I wonder if that's still under consideration.

DR. RAPPAPORT: The proposal today was our proposal for your consideration. So everything is still on the table. If people here feel that we need to do more than we've proposed, we want to hear your suggestions, your reasoning for making those recommendations, and we'll certainly take that into consideration. That's exactly why we're here today.

DR. KIRSCH: I'd like to thank all the presenters and all the members of the committee for active discussion, and I will see you tomorrow.

(Whereupon, at 4:58 p.m., the meeting was adjourned.)